Cognitive task performances as biomarkers & candidate endophenotypes in childhood neurodevelopmental disorders: ADHD & autism

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COGNITIVE TASK PERFORMANCES AS BIOMARKERS & CANDIDATE ENDOPHENOTYPES IN CHILDHOOD NEURODEVELOPMENTAL DISORDERS: ADHD & AUTISM

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Abstract

Autism spectrum disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are both defined on the basis of behavioural impairments and there is no informative biological test available for the diagnosis of the two disorders yet. The current diagnostic criteria adopt hierarchical approach and preclude the diagnoses of ADHD and ASD in an individual.

The thesis investigated whether ASD and ADHD could be discriminated based on their neuropsychological profiles. Moreover, the study explored the cognitive profile of the comorbid ASD-ADHD group. Finally, the thesis assessed whether the biomarkers represent putative endophenotype.

The findings suggested that even though the core diagnostic criteria of ADHD and ASD are entirely different, they can co-occur possibly due to shared risk. The neuropsychological data revealed that the poor inhibitory control and premature style of responding appeared to be candidate biomarkers that showed some differentiation between ADHD and ASD. Whereas, weak central coherence style as observed by a disregard for sentence context and impairment in response monitoring were in common to both disorders.

Comorbidity was not associated with a more impaired cognitive profile than the pure groups. The comorbid ASD-ADHD group showed a response inhibition deficit and a premature style of responding similar to the ADHD group; and relatively poor understanding of the stories with social content similar to the ASD group. In addition, similar to both groups, they showed impairments of response monitoring and the weak coherence style in verbal domain, which suggests similar neuropsychological correlates.

The study opened up an avenue for future endophenotype research by showing antisaccade correction rate and saccade amplitude to meet the co-familiarity criterion for a broad endophenotype that is shared across ASD and ADHD.

The study has implication for diagnosis and treatment of the two disorders and their comorbidity, and suggests that the comorbid ASD-ADHD could be a fruitful candidate for future research.

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Table of Contents

List of Tables

List of Figures

List of abbreviations

ACC: Anterior cingulate cortex

ADHD: Attention Deficit/ Hyperactivity Disorder

AS: Antisaccade

ASD: Autism Spectrum Disorder

CC: Central Coherence

CD: Conduct Disorder

CPT: Continuous Performance Test

DLPC: Dorsolateral prefrontal cortex

DTI: Diffusion tensor imaging

EP: Endophenotype

EF: Executive Function

FFA: Fusiform face area

GNG: Go/No-Go task

G-D: Goal-directed

HFA: High-Functioning Autism

HKD: Hyperkinetic Disorder

IFC: Inferior prefrontal cortex

ISV: Intra-Subject Variability

MPFC: Medial prefrontal cortex

OCD: Obsessive Compulsive Disorder

ODD: Oppositional Defiant Disorder

PDD: Pervasive Developmental Disorders

PDD-NOS: PDD-Not Otherwise Specified

PS: Prosaccade

RRIB: Restricted, repetitive interests and behaviours

RT: Reaction time

SRT: Saccade reaction time

STS: Superior temporal sulcus

ToM: Theory of Mind

Chapter 1

Introduction to Autism Spectrum Disorder and Attention Deficit/Hyperactivity Disorder

1.1 Chapter Overview

This chapter will provide an introduction to ASD and ADHD research presenting each of the key areas separately. First, important issues relating to the definition and diagnosis of each disorder will be addressed. Then, the epidemiology, clinical manifestations and cognitive approaches to each disorder will be described and the key findings of structural and functional brain changes in these conditions will be reviewed. Then the co-occurrence of ADHD and ASD and the endophenotype approach in both disorders will be briefly mentioned. The chapter will conclude with an explanation of the research problem that this thesis addresses.

1.2 Overview of Autism Spectrum Disorder (ASD)

1.2.1 Definitions, Description and Diagnosis

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterised by marked impairments in social relatedness and reciprocity, alongside impairments in the use of language for communication; and by restricted, repetitive and stereotyped patterns of behaviour.

The term 'early infantile autism' was first introduced by Leo Kanner to describe a group of children who all had 'extreme aloneness from the very beginning of life' and presented with impaired social responsiveness, an obsessive desire for the 'preservation of sameness', echolalia, poor eye contact, restricted interests, and oversensitivity to stimuli, combined with good memory and seemingly good cognitive potential (Kanner, 1943). 'Autistic psychopathy' was independently used by Hans Asperger (1944, translated by Frith, 1991) to describe four children showing a similar pattern of social withdrawal and obsessive interests. There were differences between the two descriptions; most notably Asperger observed fluent language abilities, poor motor coordination, and evidence of abstract thought (Wing, 1991).

Kanner and Asperger's early descriptions formed the basis of the description of autism as it is known today. It is recognised that autism demonstrates considerable phenotypic heterogeneity in terms of presentation and across development. Wing and Gould (1979) introduced the concept of an autistic spectrum to cover a range of ability levels and severities, all characterised by qualitative impairments in social, communication and imaginative development (Wing & Gould, 1979).

There is no informative biological test available for diagnosis. ASD is a behaviourally defined disorder and diagnosis is made based on the diagnostic criteria. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), which is recommended by the American Psychiatric Association (APA, 1994) and the International Statistical Classification of Diseases-10th Revision (ICD-10, classified by World Health Organization, 1993).

ASD characterised on the basis of a triad of behavioural impairments in the three core domains which form the basis of the current diagnostic criteria: 1) social reciprocity and engagement, 2) language and communicative skills, and 3) the presence of restricted and repetitive behaviours and stereotyped interests. These features must be evident before 3 years of age, although diagnosis is often made much later (see Table 1-1 for DSM-IV criteria and Appendix A for ICD-10 criteria).

Asperger's disorder that is a type of ASD is diagnosed on the basis of impairments in all domains of the triad as for autism, but with no clinically significant delay in language. Moreover, the individuals with Asperger's consistently have average to above average cognitive skills.

The DSM-IV currently places ASD within the category of Pervasive Developmental Disorders (PDD), which acknowledges ASD as a lifelong disorder with persistent behavioural symptoms. PDD also includes Asperger's disorder, Rett's disorder, Childhood Disintegrative Disorder (CDD) and PDD-Not Otherwise Specified (PDD-NOS). In PDD-NOS, individuals can show a pervasive impairment in any of the domains which apply to ASD; however, a diagnosis of ASD can only be made when impairments are found in all three areas. It is also important to note that in both DSM-IV and ICD-10, a diagnosis of ASD can be made only if the symptoms are not attributable to certain other developmental disorders such as Rett's disorder.

ASD is the collective term used to include the range of manifestations of the disorder, and will be used throughout this thesis to refer to individuals who have a diagnosis of Autistic Disorder, High-Functioning Autism (HFA) or Asperger's disorder.

Table 1-1: Current diagnostic criteria for Autism according to DSM-IV

A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3)
(1) Qualitative impairment in social interaction, as manifested by at least two of the following:
(a) Marked impairment in the use of multiple nonverbal behaviours such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
(b) Failure to develop peer relationships appropriate to developmental level
(c) A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
(d) Lack of social or emotional reciprocity
(2) Qualitative impairments in communication as manifested by at least one of the following:
(a) Delay in or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
(b) In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
(c) Stereotyped and repetitive use of language or idiosyncratic language
(d) Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
(3) Restricted, repetitive and stereotyped patterns of behaviour, interests and activities, as manifested by at least one of the following:
(a) Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
(b) Apparently inflexible adherence to specific, non-functional routines or rituals
(c) Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
(d) Persistent preoccupation with parts of objects
B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play
C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

1.2.2 Clinical Manifestation of ASD

ASD presents with a wide range of symptom intensity and severity. It is characterised by delayed and abnormal language development, poor social reciprocity and social communication, difficulties in imaginative play, difficulty in recognising and understanding emotions, repetitive behaviours and unusual interests.

1.2.2.1 Social Reciprocity

The most characteristic aspect of autism is difficulty in reciprocal social interaction. In the preschool years, children with autism may show a lack of interest in their peers, a limited range

of socially directed behaviours such as facial expressions and unusual eye contact. Some individuals with autism may remain uninterested in social relationships throughout their life, while others may gain some social skills as they grow up.

Previous reports on autistic individuals have shown a delay in or failure of development in three primary areas of social reciprocity including: *interpersonal relatedness*, that is a failure to coordinate affective perspectives with others, which is assumed to form the foundation of later appearing social impairment as suggested by Hobson (Hobson, 1986); *joint attention*, that is the ability to coordinate one's attention to an object with another person's (McArthur & Adamson, 1996) and *imitation*, the mimicking of facial expressions (van Lang et al., 2006), playful imitation of others, and voluntary gestural imitation (Rogers, Bennetto, McEvoy, & Pennington, 1996).

1.2.2.2 Language and Communication

Impairment in communication can range from absence of speech to adequate speech with poor conversational skills. The unique speech style characteristic of ASD includes atypical intonation or prosody (Rutter & Schopler, 1992). Communicative impairments extend into the nonverbal domain, as children and adults with ASD exhibit difficulties integrating gesture and language (Lord & Pickles, 1996; Mundy, Sigman, & Kasari, 1990).

1.2.2.3 Repetitive Behaviours and Stereotyped Interests

Individuals with ASD typically show stereotyped behaviours and interests, including a strong resistance to changes in their environment or routines; unusual preoccupations and circumscribed interests, such as train schedules or cartoon characters; repetitive use of objects, such as lining up cars; an insistence on ritualized actions; and stereotyped body movements involving the fingers and hands or the whole body. High-functioning individuals are equally likely to show these symptoms (Eigsti & Shapiro, 2003).

Rigid and repetitive behaviour and interests emerge later than social and communicative difficulties, are less good markers of autism in infancy, improve less from infancy to early childhood (Charman & Swettenham, 2001) are poorly predicted from early measures of imitation or language (Charman et al., 2003; Lord & Pickles, 1996), and respond less well to some intervention programs (Aldred, Green, & Adams, 2004).

1.2.3 Epidemiology of ASD

Through the 1980s ASDs were believed to be rare, with a prevalence of no more than 5 per 10,000 persons (Gillberg, Steffenburg, & Schaumann, 1991) and were considered more of an intriguing clinical dilemma than a major health problem. Nowadays, the prevalence of ASDs is estimated to be much greater than was previously recognised, affecting approximately 1 in 100 children and adolescents (Baird et al., 2006).

In addition to a true increase in prevalence, alternative explanations have been proposed such as broadening of the diagnostic criteria, raised public and professional awareness, different methods of ascertainment, and varying study populations, i.e. inclusion of younger age, individuals with average intelligence quotient (IQ) and those with other neuropsychiatric and medical disorders (Rutter, 2005; Williams, Higgins, & Brayne, 2006).

Boys are affected with ASDs more frequently than girls with an average male-to-female ratio of 4.3:1 (Fombonne, 2005). The sex ratio is modified substantially by cognitive impairment; among cases without intellectual impairment the sex ratio is estimated to be more than 5.5:1, whereas among those with an intellectual disability the sex ratio is closer to 2:1 (Fombonne, 2005).

The best known predictors of functional outcome in children with ASD are cognitive status, age at language acquisition, and age at diagnosis (McGovern & Sigman, 2005; Turner, Stone, Pozdol, & Coonrod, 2006). Howlin et al. in a follow up study reported that individuals with a childhood performance IQ of at least 70 had a significantly better outcome than those with an IQ below this. However, within the normal IQ range, outcome was very variable and, on an individual level, neither verbal nor performance IQ proved to be consistent prognostic indicators (Howlin, Goode, Hutton, & Rutter, 2004). Seltzer et al. found that most individuals with autism do not attain normative outcomes in adulthood and continue to manifest significant degrees of symptomatology and dependency. Only a small sub-group (about 15%) of individuals with ASD showed more favourable outcomes while 60%–75% experienced poor or very poor outcomes in their adulthood (Seltzer, Shattuck, Abbeduto, & Greenberg, 2004).

1.2.4 Genetic Epidemiology: Heritability of Autism

It is well established that ASD is highly heritable. Despite early reports that autism might follow a simple autosomal recessive inheritance model (Ritvo et al., 1985), later studies have consistently suggested more complex inheritance. The genetic mechanisms are complex and include rare chromosomal anomalies, several individual genes of major effect, and numerous common variants of small effect (Abrahams & Geschwind, 2010).

The genetic liability to autism was reported first in 1977 on the basis of a study by Folstein and Rutter comparing autistic disorder concordance in 11 monozygotic (MZ) and 10 dizygotic (DZ) twin pairs (Folstein & Rutter, 1977a). In the narrowly defined autism, they showed MZ twins were 36% concordant, whilst in DZ twins there was 0% concordance. It was also found that when criteria were widened to include individuals who show some but not all features of autism, called 'broader autism phenotype' (BAP), as described by Folstein and Rutter (Folstein & Rutter, 1977a), figures changed: MZ concordance increased to 92% and the DZ concordance increased to 10% (Bailey et al., 1995). A more recent study focusing on a broader autism phenotype reported concordance rate of 88% and 31% for MZ and DZ, respectively (Rosenberg et al., 2009).

The prevalence of ASD among siblings of individuals with ASD is estimated to be 2% - 6% (Bailey, Palferman, Heavey, & Le Couteur, 1998), much higher than contemporaneous population prevalence estimates, providing additional support for the heritability of autism. Moreover, family studies have also shown that 20% of siblings of probands with ASD may have more subtle variants of the core features of ASD referred to as BAP, which include behaviours such as aloofness, limited friendships and social interaction, poor pragmatic and reciprocal language, and preference for predictable routine (Piven, Palmer, Jacobi, Childress, & Arndt, 1997).

Taken together, twin studies and family studies have clearly established that a genetic susceptibility to autism exists. As MZ concordance is less than 100% and the degree of impairment and range of symptoms vary markedly among concordant pairs, environmental factors might likely be aetiologically significant as well (Bailey, et al., 1995; Le Couteur et al., 1996).

1.2.5 Broader Autism Phenotype

Autism has traditionally been considered as a qualitatively distinct behavioural syndrome characterised by a triad of impairments. There is, however, consistent evidence that autistic traits are continuously distributed in the general population and that ASD represents the extreme of a normally distributed continuum (Hoekstra, Bartels, Verweij, & Boomsma, 2007; Steer, Golding, & Bolton, 2010; Wheelwright, Auyeung, Allison, & Baron-Cohen, 2010).

The genetic theory of autism proposes that ASD is strongly heritable and that first-degree relatives of children with ASD possess the BAP (Bailey, et al., 1995). It is increasingly recognised, therefore, that there is a need to study dimensional as well as categorical constructs of the phenotype. Thus, based on this view, the current study adopts a quantitative approach in Chapter 8, which assumes that ASD is at the extreme end of a continuously distributed trait as are the underlying cognitive processes.

1.2.6 Associated Conditions & Comorbidities

The aetiology and pathophysiology of ASD is only partially understood. The co-occurrence of other developmental, behavioural, psychiatric, and medical conditions within ASD are commonly reported. In a small proportion of children with the condition, a specific medical disorder is identified, but the causal significance in many instances is unclear. Currently, the medical conditions that are best established as probable causes of ASD include Fragile X syndrome, Tuberous Sclerosis and abnormalities of chromosome 15 involving the 15q11-13 region (Bolton, 2009).

High rates of frontostriatal disorder comorbidity are also observed in children with ASD, although these do not always fit in with the strict diagnostic criteria. Gillberg and Billstedt have

stated that common comorbid conditions of ASD include disorders of attention, motor control and perception (DAMP), Obsessive Compulsive Disorder (OCD), Tourette's and ADHD (Gillberg & Billstedt, 2000).

There are also intellectual and behavioural problems within ASD. Intellectual disability has historically been an associated diagnosis in 70%–75% of children with ASD. However, more recent, epidemiological studies report the prevalence rates of intellectual disability in autism to be between 40% and 55% (Chakrabarti & Fombonne, 2001). Behavioural difficulties have been reported frequently in individuals with ASD which may be related to the core features of autism (e.g., perseveration, obsessiveness), comorbid diagnoses or symptoms (e.g., aggression, disruption, hyperactivity, self-injury), or sensory abnormalities. Psychiatric symptoms such as anxiety or depression may be influenced by the severity of core deficits, cognitive impairments, and/or comorbid medical disorders (Gillott, Furniss, & Walter, 2001; Lainhart & Folstein, 1994).

1.2.7 Cognitive Theories of ASD

To date, no primary deficit has been proposed to explain the full triad of social, communicative and rigid/repetitive difficulties. Current cognitive accounts of ASD can be divided into those that suggest deficits in social cognition like Theory of Mind (ToM) (Baron-Cohen, Leslie, & Frith, 1985), or social orienting (Klin, Volkmar, & Sparrow, 1992), and those that suggest deficits in non-social processes like executive dysfunction (Ozonoff, Pennington, & Rogers, 1991), 'Weak Central Coherence' (Frith, 1989a), or enhanced processing of local features (Mottron, Dawson, Soulieres, Hubert, & Burack, 2006). Here, a short description of some of those accounts pertinent to the interest of the current study is provided, with more detailed reviews appearing in the relevant chapters.

1.2.7.1 Theory of Mind Account

The 'Theory of Mind' account was primarily proposed to explain the core social, communication, and imaginative impairments seen in individuals affected by ASD (Baron-Cohen, et al., 1985). The term ToM was introduced by Premack and Woodruff (1978) to describe the ability to attribute mental states to oneself and others in order to explain and predict the behaviour of others based on their mental states (Premack & Woodruff, 1978). The ToM account hypothesises a failure of an innate system for attending to and representing mental states, such as intentions, feelings, beliefs, and desires to oneself or others and, as a consequence, causing difficulties in social interaction and communication (Baron-Cohen, et al., 1985).

The ToM account has been of huge theoretical and practical benefit in understanding and addressing the social and communicative difficulties children with ASD encounter, but it cannot

explain the whole picture of ASD by itself and there are several limitations to the explanatory power of the theory. One limitation is that a significant minority of individuals with ASD passes standard ToM tasks successfully (e.g., false belief tasks) and still presents with severe social impairments. There have also been several attempts to disapprove the ToM hypothesis by illustrating how ToM ability can be influenced by other psychological processes. Russell et al. for example demonstrated how executive function can contribute to failure in false belief tasks (Russell, Saltmarsh, & Hill, 1999).

1.2.7.2 Executive Function Account

'Executive function (EF)' is an umbrella term covering a range of higher-level capacities necessary for the control of action, especially in novel contexts, such as planning, initiation and monitoring of action, working memory, impulse control, inhibition, and mental flexibility (Hill, 2004). The executive function approach attempts to explain the social and non-social difficulties observed in ASD (Hill, 2004).

Executive impairment is not specific to autism and can be seen in a number of developmental disorders including ADHD, Tourette's syndrome, phenylketonuria, OCD, and schizophrenia (Ozonoff & Jensen, 1999; Pennington & Ozonoff, 1996; Sergeant, Geurts, & Oosterlaan, 2002); however, deficits in set-shifting and planning appear to be characteristic of ASD (Hill, 2004).

1.2.7.3 Weak Central Coherence Account

It is clear that neither ToM nor executive dysfunction would provide a unitary account of the autism behavioural phenotype. Also they fail to explain why individuals with ASD show some superior skills in certain areas and as a result alternative cognitive theories emerged. The Weak Central Coherence account has specifically tried to address both deficits and abilities in ASD (Happe & Frith, 2006) and was first suggested by Frith in 1989 (Frith, 1989a). Frith coined the term 'central coherence (CC)' for the tendency to process incoming information in its context often at the expense of memory for details. It has been suggested that the global processing predominates over local processing in at least some aspects of perception. Frith suggested that this feature of information processing is disturbed in autism, and that people with autism show detail-focused processing in which features are perceived and retained at the expense of global configuration and contextualized meaning (Frith, 1989a).

1.2.8 Structural and Functional Brain Changes in ASD

1.2.8.1 Brain Structure

The presence of structural brain changes was long postulated in autism. In 1943, when Leo Kanner first described autism in a case report of 11 patients, he noted the presence of 'relatively large heads' in a group of them. This observation was later supported by the research into the neurobiological underpinnings of autism. These studies included both children and adults, and

revealed that approximately 15%–20% of individuals with autism exhibited macrocephaly (Bailey et al., 1993; Lainhart et al., 2006).

Structural neuroimaging research has made valuable contributions to our understanding of the neuroanatomy of ASDs (for more comprehensive reviews see (Bauman & Kemper, 2005; Stigler, McDonald, Anand, Saykin, & McDougle, 2011)) and several studies have tried to explain the clinical and cognitive correlates of the structural brain changes in ASDs. A selective review of neurobiological findings in ASD at anatomical level will be presented.

Both grey and white matter abnormalities have been reported in ASDs (Carper, Moses, Tigue, & Courchesne, 2002; Muller, 2008). Abnormalities in different cortical area have been reported; among them, increased frontal lobe volume is one of the most consistent findings (Carper, et al., 2002). The cortex along the superior temporal sulcus (STS) has been found to play a role in processing eye movements (Hoffman & Haxby, 2000). Anterior and superior displacements, as well as decreased bilateral grey matter volumes of the STS in youth with autism have been reported (Boddaert et al., 2004).

The amygdala plays an important role in emotional and social behaviour (Adolphs, 2008). Volumetric research on amygdala has been inconsistent, with age emerging as a significant factor (Stigler, et al., 2011). Bilateral enlargement of the amygdala was reported in children with autism aged 1–5 years, with a positive correlation between amygdala volume and social and communication impairment in the autism group (Schumann, Barnes, Lord, & Courchesne, 2009). However, research on adolescents or adults with autism reported either no difference (Haznedar et al., 2000) or smaller amygdala volumes (Nacewicz et al., 2006).

The anterior insula has been shown to function to integrate multiple neurocognitive systems associated with affective and empathic processes (Menon & Uddin, 2010). Decreased grey matter was documented in the right insula in adults with ASDs versus healthy controls (Kosaka et al., 2010).

Research on the fusiform gyrus (FG) which is implicated in some aspects of face processing such as face identification has produced inconsistent results: volumetric studies of the FG have found unchanged, increased, or decreased volumes in adolescents and adults with ASDs (Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Toal et al., 2010; Waiter et al., 2004).

Caudate has a role in EF and has been implicated in the development of stereotyped and repetitive behaviours (Turner, Frost, Linsenbardt, McIlroy, & Muller, 2006). An increase in caudate volume, as well as a positive correlation between caudate volume and repetitive behavior, in youth and adults with autism has been observed (Brambilla et al., 2003; Rojas et al., 2006).

In summary, as Stigler reviewed, inconsistencies in the location as well as the direction (increase or decrease) of changes in brain volume could be due to the heterogeneity of ASDs, as well as differences in diagnostic criteria, individual characteristics (e.g., age, IQ, or gender) and imaging methodologies (Stigler, et al., 2011)

1.2.8.2 Brain Function

A recent review of functional MRI studies conducted by Minshew and Keller (2010) has suggested that the specialisation of many cortical networks have failed to fully develop in high-functioning individuals with autism. This finding is based upon altered connectivity evident in resting and active modes as well as evidence of altered activation in frontostriatal networks including the anterior cingulate cortex and enhanced activation/connectivity of posterior (parieto-occipital) networks (Minshew & Keller, 2010).

Brain function of people with autism has been examined in relation to specific clinical symptoms as well as using cognitive tasks such as EF, or ToM tasks as behavioural probes. In a study of response inhibition in adults with autism, decreased anterior cingulate cortex (ACC) activation has been found which suggests an atypical inhibition circuitry in individuals with autism (Thakkar et al., 2008).

Another component of EF, planning, was assessed with the Tower of London (ToL) task in an fMRI study of adults with autism. Although no significant group differences in brain activation were found, evidence of decreased connectivity was recorded between frontal and parietal areas in the individuals with autism suggesting a lower degree of information integration across certain cortical regions may contribute to the EF deficits observed in autism (Just, Cherkassky, Keller, Kana, & Minshew, 2007).

The neural basis underlying impairments in ToM in youth and adults with ASDs also has been investigated. Abnormal patterns of activation in the neural network subserving ToM, namely the medial prefrontal cortex (MPFC), STS, and right temporal pole were found (Castelli, Happe, Frith, & Frith, 2000).

In fMRI studies that employed emotionally neutral faces in an aim to assess the neural basis of face perception, individuals with autism either did not activate, or demonstrated lower activation in the fusiform face area (FFA) in response to stimuli. Moreover, the ASD group tended to exhibit greater activation in more object related brain regions (Pierce, et al., 2001).

1.2.8.3 Brain Connectivity

Recent emphasis seems to be turning towards abnormalities of brain connectivity rather than discrete areas of damage. Reduced white matter density in the corpus callosum in individuals with HFA has been reported by Chung et al. (Chung, Dalton, Alexander, & Davidson, 2004) suggesting impaired interhemispheric connectivity. Furthermore, Barnea-Goraly et al. (2004)

found reduced white matter integrity in adolescents with ASD compared to controls using diffusion tensor imaging (DTI) (Barnea-Goraly et al., 2004).

These findings of underconnectivity may be associated with unusual growth rates seen in autistic individuals (Courchesne et al., 2001). Frith proposed that a lack of pruning during the normal growth spurt may result in the presence of unnecessary connections and cause increased brain size (Frith, 2004). This process would likely impact on the connectivity between brain regions and would also affect top-down processing systems, which directly relate to integration and coherence processes (Hill & Frith, 2003).

1.2.9 Interventions and Treatment Strategies

No medications are currently available to treat the core symptoms of ASD. In general, medications are prescribed to address comorbid behaviours such as short attention span, impulsivity/hyperactivity, sleep problems, repetitive/preservative behaviours, anxious mood, agitation, aggression, and disruptive and self-injurious behaviours.

Howlin reviewed a vast range of treatments for autism, including dietary restrictions, vitamin supplementation, pharmacological interventions and early intervention techniques. Of all these treatments, only early interventions in the form of behavioural education were deemed consistently useful, with no clear support found for any of the others (Howlin, Magiati, & Charman, 2009).

The methods of interventions vary, but they tend to combine behavioural, developmental, and educational approaches to enhance cognitive, communication, and social skills of individuals with autism while minimizing autistic symptomatology and other behavioural problems. These programs can be described in three main categories: programs that have a specific focus on communication; those in which developmental/educational strategies have been employed, and those with a particular emphasis on the use of behavioural principles to improve learning and behaviour (Howlin, Magiati, & Charman, 2009).

The communication-focused interventions, such as the Picture Exchange Communication System (Bondy & Frost, 1998) were designed in an attempt to provide a communication modality for children who have no spoken language. There are other programs, designed for both nonverbal and verbal children. These programs such as parent communication training approaches (Aldred, Green, & Adams, 2004), target the early interactions between parents and newly diagnosed children with aim to enhance nonverbal and verbal communication.

1.3 Overview of Attention Deficit Hyperactivity Disorder (ADHD)

1.3.1 Definition, Description and Diagnosis of ADHD

Attention deficit hyperactivity disorder (ADHD) is a childhood neurodevelopmental disorder diagnosis based on the presence of developmentally inappropriate levels of impulsivity, hyperactivity, and inattentiveness, and consequently it has a heterogeneous behavioural profile and may have heterogeneous aetiology. In 1962 Clements and Peters described a group of children manifesting hyperactivity, poor impulse control, and short attention span and distractibility under the category of minimal brain dysfunction (Clements & Peters, 1962). However, it was not until 1968 that a disorder resembling ADHD appeared in the DSM-II (APA, 1968), when 'hyperkinetic reaction of childhood' was defined as a form of hyperactivity.

The current criteria for the diagnosis of ADHD (Table 1-2), published by the APA in the DSM-IV (APA, 1994), is now the most widely used in both clinical and research diagnoses. The DSM-IV symptoms are divided into two behavioural dimensions: hyperactive, impulsivity and inattentiveness. Therefore, based on the presentation of symptoms, the DSM-IV allows for subtyping of ADHD into a predominantly inattentive or hyperactive-impulsive subtype, or a combined subtype.

For an individual to meet DSM-IV criteria for ADHD, these symptoms need to cause impairment by the age of 7 and be present in different settings, for example at home and at school. Another classification system used mostly in Europe for diagnosis is the ICD-10 which describes hyperkinetic disorder as equivalent to a subgroup of the combined subtype of ADHD, as in DSM-IV (Barkley, 1998).

Table 1-2: Current diagnostic criteria for ADHD according to DSM-IV

(A1) Inattention: six (or more) of the following symptoms persisting for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

- often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- often has difficulty sustaining attention in tasks or play activities
- often does not seem to listen when spoken to directly
- often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)
- often has difficulty organising tasks and activities
- often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
- often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
- is often easily distracted by extraneous stimuli
- is often forgetful in daily activities

(A2) Hyperactivity-impulsivity: six (or more) of the following symptoms persisting for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

- often fidgets with hands or feet or squirms in seat
- often leaves seat in classroom or in other situations in which remaining seated is expected
- often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- often has difficulty playing or engaging in leisure activities quietly, is often "on the go" or often acts as if "driven by a motor"
- often talks excessively

Impulsivity

- often blurts out answers before questions have been completed
- often has difficulty awaiting turn
- often interrupts or intrudes on others (e.g., butts into conversations or games)

Other criteria for diagnosis:

(B) Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

(C) Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

(D) There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

(E) The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or Personality Disorder).

1.3.2 Clinical Manifestation of ADHD

The characteristic symptoms of ADHD are excessive motor activity, inattentiveness, and impulsivity. Compared with their peers, these children seem to be fidgety and restless in the situations where they are required to be still and quiet. These symptoms can be present both in structured situations, such as the classroom, and in unstructured situations, such as the home or playground. The extent of behavioural impairments varies with the demands of the situation. For example, a child who is highly symptomatic at school maybe quite average while interacting with peers.

1.3.2.1 Inattentiveness

Inattention is one of the hallmarks of ADHD. Children have difficulty sustaining their attention and find it hard to remain focused on a task, as they are often easily distracted by extraneous stimuli. They have difficulties following the instructions and they fail to give close attention to detail. At school, their work is characterised by careless errors, forgetfulness, and poor organization.

1.3.2.2 Impulsivity

Impulsiveness can be presented by having difficulty waiting for their turn in the queue, interrupting others' conversation or blurting out answers before questions are completed.

1.3.2.3 Hyperactivity

Children with ADHD are fidgety or squirm in their seats. They are described by their parents as always being on the go or often acting as if "driven by a motor". They may leave their seats in the classroom or in other situations where they are expected to remain seated.

The manifestations of ADHD change across development. During preschool years, overactivity is most prominent. Inattention becomes more obvious during school years, and as the child reaches adolescence and adulthood, the motor activity diminishes, and inattention and impulsivity become more salient and impairing, especially during social interaction.

1.3.3 Epidemiology of ADHD

ADHD is one of the most prevalent conditions in child psychiatry. The prevalence of ADHD among children is estimated to be around 3–10% (Faraone, Sergeant, Gillberg, & Biederman, 2003) depending on the measure used and the population sampled. Faraone and colleagues showed that the discrepancy in prevalence is mostly due to differential diagnostic criteria rather than true prevalence differences between countries. Also they relate the variation in the apparent prevalence rate to the population surveyed (Faraone, et al., 2003) as the community samples give higher prevalence rates than school samples (mean prevalence: 10.3% for community samples vs. 6.9% for school samples) (Brown et al., 2001). Generally, countries that

employ DSM criteria find impairment in 5-10% of the population and those using ICD criteria have a prevalence of 1-2% (Rohde et al., 2005), as the ICD-10 diagnosis of hyperkinetic disorder represents only a more severe subset of DSM-IV ADHD.

The disorder persists into adult life, though it lessens with age. Faraone et al. (Faraone, Biederman, & Mick, 2006) in a meta-analysis regression model assessed the syndromatic and symptomatic persistence of ADHD from the published literature separately. They reported the rate of syndromatic persistence (individuals meeting full criteria for ADHD) to be quite low (15% at age 25), while the rate of symptomatic persistence (individuals meeting subthreshold criteria for ADHD) was much higher (65%).

Boys are five times more often affected than girls (Ford, Goodman, & Meltzer, 2003). The aetiology underlying this gender bias is not clear yet.

1.3.4 Genetic Epidemiology: Heritability of ADHD

ADHD is a familial condition with a complex pattern of inheritance. Twin and adoption studies demonstrate the important role of genetic factors in individual differences for ADHD, with multiple genetic factors thought to interact with environmental risks (Asherson, Kuntsi, & Taylor, 2005).

Recent estimates suggest a four to six fold increase in ADHD risk among first-degree relatives of individuals with ADHD (Faraone, Biederman, & Monuteaux, 2000). Twin studies using parent and teacher rating scales of ADHD found heritability estimates of about 60-90% (Faraone et al., 2005). Molecular genetic studies have identified several genes associated with ADHD, such as dopamine and related monoamine neurotransmitter genes, in particular the variants of dopamine transporter D4 and D5 receptor genes (Faraone, et al., 2005).

1.3.5 ADHD: Quantitative Traits

ADHD, as defined by DSM-IV, is a dichotomous trait making up a distinct diagnostic category. However, there has been ongoing debate about whether it could be better conceptualized dimensionally or categorically. There is consistent evidence from community cohorts and twin studies that measures of hyperactivity, impulsivity, and inattention are continuously distributed quantitative traits in the general population (Biederman et al., 1993; Boyle et al., 1997; Goodman & Stevenson, 1989; Thapar, Harrington, Ross, & McGuffin, 2000). Furthermore, both twin and sibling data indicate that the genetic contribution to ADHD is the same across the continuum and in the extreme ADHD scores (Chen et al., 2008; Levy, Hay, McStephen, Wood, & Waldman, 1997).

Based on this view, the current study adopts a quantitative approach in Chapter 8, which assumes that ADHD is at the extreme end of a continuously distributed trait as are the underlying cognitive processes.

1.3.6 Associated Conditions & Comorbidities

Children diagnosed with ADHD experience serious academic, social, and psychological impairment across development. ADHD may lead to low self-esteem, poor peer relationships, delinquencies, and substance abuse. It is estimated that around 60–100% of patients with ADHD also have one or more comorbid disorders (Gillberg et al., 2004) which often continue into adulthood (Biederman, 2004).

In 2001, Kadesjo and Gillberg presented a paper which suggested that "it is the exception not the rule, to encounter cases with 'pure' ADHD" (p. 491). There are many examples of ADHD being comorbid with other frontostriatal disorders such as conduct disorder (CD), OCD, Tourette's disorder, and oppositional defiant disorder (ODD) (Kadesjo & Gillberg, 2001).

There is evidence of clinical and neurocognitive overlap between psychosis and ADHD (Bellak, Kay, & Opler, 1987; Stahlberg, Soderstrom, Rastam, & Gillberg, 2004) and in a study by Ettinger et al. (2006), an association between subclinical schizophrenia-like and ADHD-like features in psychiatrically and medically healthy men was reported (Ettinger, Joober, R, & O'Driscoll G, 2006).

Dyslexia (25–40%), motor coordination problems (50%), dyscalculia (10–60%), and sleep disorders (25–50%) are frequently observed in patients with ADHD (Gillberg, et al., 2004; Owens, 2005; Willcutt, Pennington, Olson, Chhabildas, & Hulslander, 2005). Disorders characterised by externalizing behavioural problems, such as aggressive behaviour, difficulty with authority or lying, stealing, and vandalism, ODD and/or CD have been reported in 42–90% of individuals with ADHD (Angold, Costello, & Erkanli, 1999; Cunningham & Boyle, 2002; Gillberg, et al., 2004). Furthermore, around 13–51% of ADHD patients suffer from internalising disorders, such as anxiety or depression (Angold, et al., 1999; Bauermeister et al., 2007; Gillberg, et al., 2004).

Several studies have demonstrated that ADHD patients with comorbid problems appear to have a more severe form of ADHD, are often more impaired in their daily functioning, and have a poorer long term prognosis (Bauermeister, et al., 2007; Gillberg, et al., 2004).

1.3.7 Cognitive Approaches to ADHD

One approach to understanding the aetiology of ADHD is to explore brain function through performance on cognitive tasks that explain the underlying cognitive processes. Cognitive theories vary in whether they suggest a single underlying cause for the behavioural and cognitive impairments associated with ADHD or, alternatively, multiple aetiological pathways.

Here a brief overview on the most influential accounts is provided. Full descriptions of these accounts will be discussed in the relevant chapters.

1.3.7.1 Executive Function Account

The executive dysfunction account is one of the commonly noted theories trying to explain ADHD at the cognitive level. Barkley in 1997 argued that poor inhibition impairs one's ability to prevent irrelevant responses, resist interference, and execute complex sequences of responses. The hypothesis that a core deficit in response inhibition leads to deficits in other executive functions has been particularly influential (Barkley, 1997, 1998).

In a meta-analysis of 83 studies of executive functioning in childhood ADHD by Willcutt et al. (2005), they summarized that the most consistent deficits were in measures of response inhibition, vigilance, working memory, and planning. They showed that weaknesses in EF were significant in both clinic-referred and community samples which were not explained by group differences in intelligence, academic achievement, or symptoms of other disorders. They concluded that moderate effect sizes and lack of universality of EF deficits among individuals with ADHD suggested that EF impairments are neither necessary nor sufficient to cause all cases of ADHD, but that these impairments appear to be one important component of the complex neuropsychology of ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

However, similar to the ASD literature, there are also studies which failed to replicate executive deficits in ADHD. For example, Kuntsi and colleagues suggested that impaired cognitive performances in ADHD are not restricted to EF; rather there is a more general behavioural dysfunction including impairment in attentional alerting, orienting, response preparation, and control (Kuntsi, McLoughlin, & Asherson, 2006).

1.3.7.2 Aspects of Attention

Attention is a multifactorial construct and multiple aspects of attention have been investigated in ADHD. Selective attention refers to the ability to attend to relevant information while ignoring irrelevant stimuli (Parasuraman, 1998). A study that applied a load-dependent attention paradigm indicated that selective attention was normal in ADHD (Huang-Pollock, Nigg, & Carr, 2005). Spatial selection and temporal non-spatial tasks similarly did not indicate impairments in the basic mechanisms of selective attention in ADHD (Mason, Humphreys, & Kent, 2005; Mason, Humphreys, & Kent, 2003).

Sustained attention refers to the ability to maintain a stable performance level over time (Parasuraman, 1998). In attention research, errors of omission (failure to detect the target stimulus) are interpreted as sustained inattention symptoms, whereas commission errors are assumed to reflect a lack of inhibition or impulsivity (Corkum & Siegel, 1993). On Go/No-Go (GNG) tasks, greater group differences between ADHD and healthy controls for omission errors would indicate a sustained attention deficit, and greater group differences for commission errors would indicate a response inhibition deficit. Previous studies found that children with

ADHD show decreased accuracy in their task performance, showing more omission and commission errors compared to the controls (Kalff et al., 2005; Swaab-Barneveld et al., 2000).

Although, attentional difficulty is one of the prominent accounts trying to explain ADHD behavioural symptoms, it does not appear to be highly specific to children with ADHD, as various other clinical groups, such as children with ASD, conduct disorder, and mood and anxiety disorders also show similar deficits (Pennington & Ozonoff, 1996; Swaab-Barneveld, et al., 2000).

1.3.7.3 Reward Processing

Several theoretical accounts of ADHD have focused on aspects of reward processing. At the behavioural level, children with ADHD often show a preference for small, immediate rewards over large, delayed ones (Scheres et al., 2006). There is evidence for an incentive-related improvement in task performance in ADHD, as indexed by reaction time (RT) measures (Andreou et al., 2007).

Many studies have found effects for reward on task performance in ADHD; however, the findings are inconsistent. Some studies have indicated that response inhibition deficits diminish following the introduction of rewards (Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Michel, Kerns, & Mateer, 2005), while others do not find this (Oosterlaan & Sergeant, 1998; Stevens, Quittner, Zuckerman, & Moore, 2002). Shanahan et al. found that children with ADHD performed worse than controls in response inhibition, irrespective of incentives (Shanahan, Pennington, & Willcutt, 2008).

1.3.7.4 Intra-Subject Variability (ISV)

Another abnormality that has been replicated highly consistently in ADHD is the increased intra-subject reaction time variability (RTSD), or intra-subject variability (ISV) (Klein, Wendling, Huettner, Ruder, & Peper, 2006; Kuntsi, McLoughlin, et al., 2006).

In some studies, this emerged initially as a 'side' finding, when other cognitive variables failed to distinguish between the ADHD and control group (Kuntsi, Oosterlaan, & Stevenson, 2001; Kuntsi & Stevenson, 2001). Kuntsi in a study on a sample of 51 pervasively hyperactive children and 119 controls showed that there was a significant difference between groups on some of the working memory tasks which then disappeared when they controlled for IQ. However, they found evidence of a pattern of responding on the Stop task that was strongly characteristic of hyperactivity as they were variable in their speed, and generally slow and inaccurate in responding (Kuntsi, et al., 2001).

Based on a psychometric analysis of different parameters of ISV in patients with ADHD using the Continuous Performance Test (CPT), Go/No-Go task, Stop Signal Task, as well as N-back tasks performance, Klein et al. indicated that the largest effect sizes emerged for indices of ISV,

such as reaction time variability. The authors concluded that across a variety of neuropsychological tests, measures of ISV contribute best to group discrimination (Klein, et al., 2006).

The theoretical underpinning of ISV in ADHD is still not clear. There are some suggestions including: a temporal processing deficit (Castellanos & Tannock, 2002), a deficit in the ability to appropriately modulate very low-frequency fluctuations in neuronal activity (Castellanos et al., 2005) and inefficiency in the use of attention by executive control processes (Bellgrove, Hawi, Kirley, Gill, & Robertson, 2005).

Moreover, it can be due to a nonoptimal arousal state that leads to inconsistent performance across different cognitive tasks, reflected in high reaction time variability and error rates. Based on this view, the modification of factors such as the presentation rate of stimuli (Sergeant, Geurts, Huijbregts, Scheres, & Oosterlaan, 2003) or rewards (Konrad, Gauggel, Manz, & Scholl, 2000) or both (Andreou, et al., 2007) can improve the performance of children with ADHD to, or near to, the level of control children.

The children with hyperactivity are not only more variable in their reaction times, but they are also generally slower and make more errors. This pattern of responding (slow, variable, and inaccurate) agrees with the pattern van der Meere identified in his review as characteristic of hyperactivity (van der Meere, Gunning, & Stemerdink, 1996). Children with ADHD seem to have frequent lapses in attention and are often inconsistent in how they perform. This might be the cause of the observed variability within and between tasks across different reaction time (RT) tasks (Geurts et al., 2008).

1.3.8 Structural and Functional Brain Changes in ADHD

1.3.8.1 Brain Structure

Structural neuroimaging research has attempted to reveal the brain regions implicated in ADHD. Alterations in the frontal lobes of children with ADHD including the precentral gyrus, the posterior cingulate, and superior and dorsolateral prefrontal grey matter have been identified in structural neuroimaging studies (Filipek et al., 1997; Hill et al., 2003).

Consistent abnormalities in inferior frontostriatal and frontocerebellar circuitries have been reported. Reduced volume and cortical thickness in inferior prefrontal cortex (IFC) as well as other frontal brain regions, parieto-temporal regions, the basal ganglia (Castellanos et al., 2001), the splenium of the corpus callosum, and the cerebellum has been found in structural MRIs (Castellanos et al., 2002; Krain & Castellanos, 2006; Mackie et al., 2007; Shaw et al., 2006).

Moreover, the presence of a relationship between performance in inhibitory tasks and fronto-striatal volume suggests a close association between the structural development of the fronto-cortical systems and cognitive functions implicated in ADHD symptoms (Batty et al., 2010)

Diffusion tensor imaging (DTI) studies have also provided evidence for abnormalities at the neural network level, showing abnormalities in multiple white matter tracts in cingulate and frontostriatal, as well as frontoparietal, frontocerebellar, and parieto-occipital white matter tracts, in children, as well as adults with ADHD (Ashtari et al., 2005).

Longitudinal studies in ADHD have indicated a developmental delay of cortical thickness trajectories most markedly for the frontal lobes (Shaw et al., 2007) (see Figure 1-1). Shaw demonstrated the median age by which 50% of the cortical points attained peak thickness to be 10.5 years for ADHD and 7.5 years for controls. The area with the greatest age difference was the middle prefrontal cortex, reaching peak thickness at 10.9 years in those with ADHD and 5.9 years for controls.

Clinical improvement is often mirrored by a convergence of developmental trajectories toward typical development; conversely, persistence of ADHD is accompanied by a progressive divergence away from typical development (Giedd & Rapoport, 2010). For example, Shaw found right parietal cortical normalization associated with clinical improvement (Shaw, et al., 2006), whereas Mackie found progressive volume loss of the inferior posterior lobes in cerebellum mirrors persistence of ADHD (Mackie, et al., 2007).

How treatment affects the brain development has been widely studied in ADHD. Earlier studies indicated that stimulants have a normalising influence on subcortical and white matter development (Castellanos, et al., 2002); however, recent studies have extended the normalising effect of treatment to cortical development (Shaw et al., 2009).

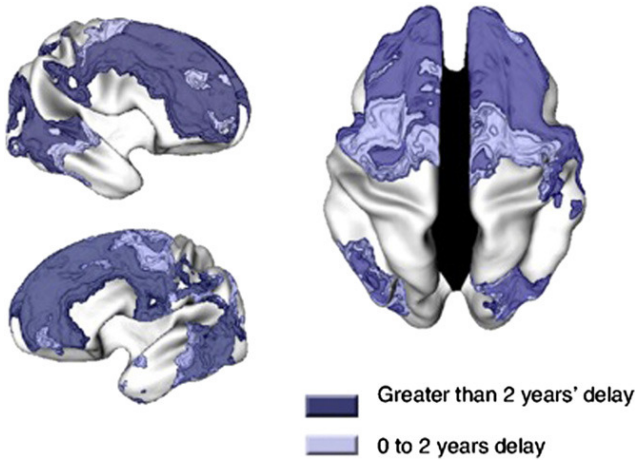


Figure 1-1: Developmental delay of cortical thickness in ADHD

Regions where the ADHD group had delayed cortical maturation (Figure from (Shaw, et al., 2007)).

1.3.8.2 Brain Function

The aim of using fMRI in ADHD research is to try to illuminate the neural mechanisms underlying behavioural difficulties observed in the disorder.

Different patterns of activation in the prefrontal cortex of children performing inhibition tasks (Rubia et al., 1999) and a failure to activate the anterior cingulate during inhibition task in adults with ADHD (Bush et al., 1999) has been observed.

Functional imaging studies have shown reduced activation compared with control individuals, in particular in the inferior prefrontal cortex (IFC), anterior cingulate, and caudate, but also in temporoparietal regions, during tasks of motor response inhibition (Durston et al., 2003; Rubia et al., 2008; Rubia, et al., 1999), interference inhibition (Rubia, Halari, Smith, et al., 2009), and of sustained, selective, and flexible attention (Rubia, Smith, Brammer, & Taylor, 2007; Rubia, Smith, et al., 2009; Smith, Taylor, Brammer, Toone, & Rubia, 2006).

Moreover, ADHD children have shown reduced activation in dorsal and ventrolateral prefrontal, cingulate, and cerebellar brain regions during temporal processes, including tasks of motor timing, time discrimination, and temporal foresight (Rubia, Halari, Christakou, & Taylor, 2009; Rubia, et al., 1999; Rubia, Taylor, et al., 2001; Smith, Taylor, Brammer, Halari, & Rubia, 2008), as well as temporal unpredictability (Durston et al., 2007).

1.3.8.3 Brain Connectivity

A reduced degree of functional connectivity relative to healthy controls has also been reported in individuals with ADHD. Rubia et al. showed reduced connectivity between IFC and the basal ganglia, parietal lobes, and cerebellum, as well as between cerebellum and parietal and striatal brain regions during sustained attention (Rubia, Halari, Cubillo, et al., 2009); and in another study, reduced connectivity has been shown between frontoparietal and frontocerebellar regions during interference inhibition and time estimation, respectively (Vloet et al.).

These findings suggest that the dysfunctions observed in individual ADHD patients not only affect isolated brain regions but also the functional interregional interconnectivity between affected regions, thus demonstrating deficits in fronto-striato-cerebellar and frontoparietal neural networks (Rubia, 2010).

1.3.9 Treatment

There is consensus over treatment approaches in ADHD that the primary treatment is medication and that accessory symptoms are benefited by multimodal treatment. Stimulants (e.g. Methylphenidate) are still the most widely used and effective treatment of ADHD, minimizing disruptive symptoms and improving the task performance (Pliszka, 2007). The expectation is that 70% of patients will respond to the first stimulant that is tried with the

recommendation that a second be tried to yield up to an 80% benefit (Elia, Ambrosini, & Rapoport, 1999).

Stimulants are quite safe, but about 20% of children with ADHD fail to respond or show significant side effects. In these situations, non-stimulants (e.g. Atomoxetine) as second-line treatments have come into consideration. It is only in ADHD individuals with an active substance abuse problem, comorbid anxiety, or tics that non-stimulants are the first-line treatment (Pliszka, 2007).

1.4 Co-occurrence of ADHD & Autism

Traditionally, a diagnosis of both ADHD and ASD in an individual has been precluded in ICD-10 and DSM-IV because of the hierarchical approach to classification that they adopt. However, recently it has been recognized that individuals with ASD often present with associated hyperactivity, inattentiveness, and impulsivity suggesting that they may in addition suffer from ADHD (Leyfer et al., 2006). Similarly, individuals with ADHD not uncommonly present with symptoms of ASD exhibiting social difficulties in a degree comparable to ASD (Clark, Feehan, Tinline, & Vostanis, 1999; Greene et al., 1996; Santosh & Mijovic, 2004).

Very little is known about what causes the association between ASD and ADHD. As yet, it is unclear whether their overlap in symptomatology reflects true co-morbidity between the disorders of ASD and ADHD or some other phenomenon.

In Chapter 2, background information about the concept of comorbidity will be provided and the current research on ADHD and ASD comorbidity will be reviewed.

1.5 Endophenotype Approach

The concept of the endophenotype was first introduced to psychiatry by Gottesman and Shields in 1973 and was described as internal phenotypes discoverable by a 'biochemical test or microscopic examination' (Gottesman & Shields, 1973) and has emerged as an important concept in the study of complex neuropsychiatric diseases.

Endophenotypes are measurable components along the pathway between disease and distal genotype and represent simpler clues to genetic underpinnings than the disease syndrome itself. However, to be most useful, endophenotypes for psychiatric disorders must meet certain criteria as Gottesman proposed: they should be heritable, co-segregate with a psychiatric illness, yet be present even when the disease is not (i.e. state independent), and be found in non-affected family members at a higher rate than in the population (Gottesman & Gould, 2003).

Many studies have focused on neurocognitive features of the disorder in the first-degree relatives of individuals with autism and ADHD in search for endophenotype candidates in these two disorders.

Chapter 9 will provide background information and further details on the concept of the endophenotype and the research carried out in ADHD and ASD.

1.6 Conclusion

The above overview points to the heterogeneous picture of both ASD and ADHD at the behavioural, clinical, anatomical, and genetic levels. There is no informative biological test available for the diagnosis of these two child neurodevelopmental disorders yet and at present they are both defined on the basis of behavioural impairments. Considering the heterogeneous profiles of ADHD and ASD, it is important to ascertain a good phenotypic definition for aetiological investigations; this consequently would affect the accuracy of estimates of prevalence rates of the disorders.

Investigations into the neurophysiological basis of ASD and ADHD have increased in recent years and it is hoped that future diagnostic techniques will be able to include genetic, neuroimaging, and neurochemical markers; however, challenges still remain for cognitive theories of ASD and ADHD.

Overall, the cognitive findings in ADHD and ASD indicate a more general deficit rather than single, specific cognitive function. The proposed deficits may not be mutually exclusive; they could all have common grounds, or equally they could represent distinctive aetiological pathways.

As mentioned above, there is some overlap in the cognitive theories trying to explain ADHD and ASD and their specificity to one disorder or another and their ability to discriminate the two disorders is not clear yet. However, these cognitive biomarkers may have utility in various clinical settings for the assessment and diagnosis of childhood onset neurodevelopmental disorders (e.g. use as early pre-symptomatic diagnostic marker and also as diagnostic tools in complex and borderline cases) and it is essential to investigate them in a methodologically controlled condition.

As it is essential to investigate these biomarkers in a methodologically controlled condition, this thesis will focus on the cognitive measures which had already been validated by showing case-control differences for ADHD and ASD in previous studies in the hope of finding reliable cognitive biomarkers. This hopefully will enable response to these questions: a) whether individuals with ADHD or ASD show any impairment in cognitive measures compared to control group, b) whether there are any similarities or differences in the performance of two clinical groups, and c) whether there are any types of assessment that can help to discriminate between ASD and ADHD. This might help to explain the cognitive nature of each disorder separately.

Little attention has been paid to the comorbidity issue between ADHD and ASD which maybe due to the fact that current criteria preclude the comorbid diagnosis to be made. This thesis also included a group of individuals with a diagnosis of comorbid ASD and ADHD with the aim to better understand the basis for the comorbidity between ASD and ADHD and to see whether the cognitive profile of comorbid cases is more similar to either ADHD or ASD group or is a mixed pattern. This would in turn help to examine whether there are any types of assessment that can be a means of identifying children with a comorbid ASD-ADHD diagnosis.

Finally, this thesis aim to study a group of siblings in the same cognitive measures administered in clinical groups and controls to test: a) whether the biomarkers represent an endophenotype, and whether there is evidence for correlations between the liabilities to the familialities of autistic traits and ADHD traits as well as 'biomarkers' of disease susceptibility/effect, and b) whether the 'putative cognitive biomarker' index the sub threshold/dimensional traits observed in siblings.

For these purposes, the present thesis focused on the three influential cognitive accounts of ASD and/or ADHD including Executive Function (EF), Theory of Mind (ToM), and Weak Central Coherence (WCC) accounts in order to investigate the extent to which the cognitive phenotype associated with ADHD overlaps with the cognitive phenotype associated with ASD and whether ADHD and ASD have shared and unique cognitive processes. To this end, established cognitive markers of ASD (e.g. EF, ToM, and CC measures), and of ADHD (e.g. EF measures such as response inhibition) were examined and this was achieved by the development of an extensive task battery designed to assess group differences in each account. Three clinical groups including children and adolescents with a diagnosis of ASD and/or ADHD were compared to a group of age-matched controls (8 to 16 years). A small group of siblings were also selected in order to assess the endophenotype hypothesis.

1.7 Overview of the Following Chapters

In Chapter 2, the background information about the concept of comorbidity will be provided and the current research on ADHD and ASD comorbidity will be reviewed. The general methodology used in the study is presented in Chapter 3.

Sample characteristics will be briefly explained in Chapter 4. As the whole test battery was not administered to all the participants, the characteristics of the sample will be also presented separately for each individual task in the relevant chapters.

Details of individual tasks and experimental findings are presented in Chapter 5 to Chapter 7 adopting a categorical approach.

Chapter 5 presents a review of the current status of the Executive Function account, documenting empirical evidence for and against this theory as a possible cognitive marker for

ASD and ADHD. The measures used to test EF account were Go/No-Go and antisaccade tasks.

The focus of Chapter 6 will be on the Theory of Mind account. The tasks were selected to assess this theory were the Triangle Task, Strange Stories and a Cueing task.

Chapter 7 is dedicated to the Weak Central Coherence account, one of the prominent theories suggested to explain autistic symptomatology both in terms of strengths and weaknesses. The tasks administered in this section included Embedded Figures, Sentence Completion, and Block Design Tasks.

Chapter 8 adopts a quantitative/dimensional approach assuming that both ASD and ADHD are at the extreme end of continuously distributed traits as are the underlying cognitive processes.

A small group of siblings were recruited and assessed in order to investigate whether the cognitive measures administered in the current study can be a reliable endophenotype. The findings from siblings will be presented separately in Chapter 9.

Chapter 2

Comorbidity

2.1 Chapter Overview

Traditionally, a diagnosis of both ADHD and ASD in an individual has been precluded in ICD-10 and DSM-IV because of the hierarchical approach to classification that they adopt. However, recently it has been recognized that individuals with ASD often present with associated hyperactivity, inattentiveness, and impulsivity suggesting that they may in addition suffer from ADHD (Leyfer, et al., 2006). Similarly, individuals with ADHD not uncommonly present with symptoms of ASD (Clark, et al., 1999).

Very little is known about what causes the association between ASD and ADHD; and as yet, it is unclear whether their overlap in symptomatology reflects true co-morbidity between the two disorders or other phenomenon.

This chapter will provide an overview on the current research in ASD and ADHD comorbidity. First, important issues relating to the definition of comorbidity, the significance and the key considerations will be discussed. And finally the current studies on ADHD and ASD comorbidity will be addressed.

2.2 Comorbidity

2.2.1 Definition

Comorbidity refers to the co-occurrence of two diagnoses at the same time for a single patient, independently of aetiological and/or pathway considerations (Rothenberger, Banaschewski, Becker, & Roessner, 2010). Several studies have reported substantial comorbidity for psychiatric disorders (Biederman, Newcorn, & Sprich, 1991; Caron & Rutter, 1991). In children's neuropsychiatric disorders, comorbidity plays an even greater role than in adults: about 80% of children develop at least one comorbid condition compared with 45% in adults (Cramer, Waldorp, van der Maas, & Borsboom, 2010; Gillberg, et al., 2004).

2.2.2 The Importance of Comorbidity

Comorbidity has begun to emerge as an important issue in recent research literature as it may lead to a better understanding of psychopathology. There are several reasons that signify the importance of taking into account comorbidity in clinic and research.

First, a study of condition A may produce findings that in fact are largely a consequence of the ignored comorbid condition B. Secondly, if comorbidity is ignored, the implicit assumption is made that the meaning of condition A is the same regardless of the presence or absence of

condition B that it can be quite an unsafe assumption in some circumstances (Caron & Rutter, 1991).

In terms of diagnosis and treatment, the individual may not benefit fully from the treatment of condition A, if the clinician fails to diagnose and treat the ignored comorbid condition B. Comorbidity is consistently associated with a greater demand for professional help, greater interference with everyday life, a poorer prognosis, and higher suicide rates (Albert, Rosso, Maina, & Bogetto, 2008; Schoevers, Deeg, van Tilburg, & Beekman, 2005) that also highlights the importance of paying attention to comorbid condition/s.

In children it is highly important to determine whether or not the coexistence of two mental disorders represents a separate clinical entity i.e., true comorbidity. Before focusing on the literatures on ASD and ADHD comorbidity, it is necessary to note the ways in which comorbidity can be the product of artefacts. It is also important to note and discuss some of the nosological considerations that apply to comorbidity.

2.2.3 Artefacts or Genuine Comorbidity

Some of the reported comorbidity may be due to possible artefacts or may reflect biases (discussed below), however genuine comorbidity raises several important research questions need to be addressed mainly at the nosological level.

2.2.4 Possible Artefacts

Possible artefacts such as referral and screening biases can produce a false picture of comorbidity. They will be briefly discussed below.

2.2.4.1 Co-occurrence by Chance

One explanation for the appearance of two disorders within the same individual is simply chance. If the two disorders are independent, with prevalences of p and q, then the expected rate of the comorbid cases should arise with the frequency of pq. In this model, individuals with one disorder do not on average have any increase risk of second disorder (Neale & Kendler, 1995). In this situation the observed rate of co-occurrence in epidemiological studies can be of help to investigate whether the observed rate is greater than the expected rate which would suggest the presence of comorbidity.

2.2.4.2 Referral Factors

Referral factors may distort clinical data on comorbidity. There is a very well-known bias, the Berkson effect (Berkson, 1946), by which the comorbidity rate in clinic samples always reported to be greater than that in the general population as individuals with more than one disorder are more likely to be referred and be part of a clinical sample.

2.2.4.3 Non-random Sampling

Another source of bias in the estimation of comorbidity rates is that clinical samples do not consist of a random sample of those who meet criteria within the population. Individuals with a greater number and severity of symptoms would be more likely to receive treatment and thus be part of an enriched sample (Neale & Kendler, 1995).

2.2.5 Nosological Considerations

As mentioned earlier, genuine comorbidity raises several important research questions mainly at the nosological level. Some of the related issues are discussed below.

2.2.5.1 Categories or Dimensions

One possibility is that the concept of disorder categories may itself be misconceived. One suggestion is that disorders involve no qualitative discontinuity between abnormality and normality but rather a pattern resulting from quantitative variations on a range of behavioural dimensions (Caron & Rutter, 1991). In this view, the extent of apparent comorbidity would be much affected by the particular cut-off points used to define disorder.

2.2.5.2 Overlapping Diagnostic Criteria

A second type of nosological confusion arrives from the fact that the same item of behaviour appears in the list of diagnostic criteria for several different diagnostic categories (Caron & Rutter, 1991). This would lead to a degree of artifactual comorbidity. For example, agitation is one of the criteria for anxiety, depression, and attention deficit/hyperactivity disorder. This does not seem to explain the co-occurrence of ADHD and ASD as their core diagnostic criteria is totally different.

2.2.5.3 One Disorder Represents an Early Manifestation of the other

Another possibility is that one disorder is an early manifestation of the other (Caron & Rutter, 1991). In child psychiatry, there are several disorders of this kind. For example, oppositional defiant disorder (ODD) often appears to be a precursor of conduct disorder (CD) or again, conduct disorder in childhood is an established precursor of antisocial personality disorder in adult life (APA, 1994).

Thus, if condition A is a precursor of B, it must be the case that the presence of A at time 1 increases the likelihood of B at time 2; and that B never precedes A. However, equally, it is to be expected that only some cases of A will develop into B and, if there is more than one precursor of B, there may be instances of B that have not been preceded by A.

Both ADHD and ASD are childhood neurodevelopmental disorders, with an early onset, so their age of onset and developmental progression do not support a possible model of one disorder leading to the other.

2.2.5.4 One Disorder is Part of the other

It may also be suggested that one disorder is part of or a secondary manifestation of the other conditions (Caron & Rutter, 1991). For example, DSM-IV precludes the diagnosis of ADHD if there is a diagnosis of ASD on the basis of the fact that the symptoms characteristic of ADHD disorders are of the symptomatology of autism.

2.2.6 Evidence for Comorbidity in ADHD and ASD

Until recently, the issue of comorbidity between ADHD and ASD has been largely neglected. As mentioned earlier, both ICD-10 and DSM-IV adopt a strict hierarchical approach to ADHD and ASD, excluding a diagnosis of AD/HD if symptoms of inattention and hyperactivity occur during the course of ASD. However, in the clinical practice, it is commonly observed that children with ASD have symptoms of ADHD and vice versa, although their core diagnostic symptoms do not overlap. Interestingly, ADHD has been shown to be the second most common comorbid disorder in individuals diagnosed with ASD (Simonoff et al., 2008)

With a growing number of studies reporting children who meet criteria for both disorders, the validity and clinical efficacy of excluding a comorbid diagnosis of ADHD and ASD have been questioned (Clark, et al., 1999; Gillberg & Billstedt, 2000; Goldstein & Schwebach, 2004; Yoshida & Uchiyama, 2004), and there are recommendations for a revision in the diagnostic criteria to allow comorbid diagnoses of autism and ADHD in the upcoming DSM-V and ICD-11 (Goldstein & Schwebach, 2004; Reiersen & Todd, 2008).

A large percentage (65–80%) of children with ADHD portrays symptoms in the autistic spectrum (Clark, et al., 1999; Gillberg, et al., 2004). Clinical studies examining comorbidity in children diagnosed with ASD have reported the presence of ADHD symptoms, sufficient to meet the diagnostic threshold for the disorder, in between 41-78% (Gadow, DeVincent, & Pomeroy, 2006; Goldstein & Schwebach, 2004; Sturm, Fernell, & Gillberg, 2004; Yoshida & Uchiyama, 2004).

The studies which have examined AD/HD symptom in autism group have found that symptoms of inattention are significantly more pronounced than symptoms of hyperactivity (Goldstein & Schwebach, 2004; Sturm, et al., 2004; Yoshida & Uchiyama, 2004). For example, Sturm described attention deficits in 95% of the children with HFA, while hyperactivity was noted in 56% of them (Sturm, et al., 2004).

These clinical studies clearly suggest the co-existence of the two disorders, however in order to decide whether the dual diagnosis of autism and ADHD is a genuine comorbidity, the existence of such comorbidity needs to be demonstrated through a number of different approaches such as evidence from theoretical domains and, further, from neurobiological and neuropsychological

studies (Gargaro, Rinehart, Bradshaw, Tonge, & Sheppard, 2011) and also evidence from genetic studies.

A crucial question is whether the inattention and hyperactivity seen in autism spectrum disorders differ qualitatively from the inattention and hyperactivity associated with ADHD.

2.2.6.1 Cognitive Profile of Individuals with Comorbid ADHD and ASD

The published research has consistently demonstrated neuropsychological impairments in individuals with ASD and those with ADHD. There have been a few studies that have compared cognitive profiles in individuals with ASD and ADHD in an attempt to identify cognitive deficits that are specific to each disorder.

As mentioned in Chapter 1, executive function deficit is one of the main accounts to explain autism symptomatology (Pennington & Ozonoff, 1996). Executive dysfunction has been also observed in individuals with ADHD (Barkley, 1997, 1998) although the pattern of dysfunction differs. Ozonoff and Jensen (1999) suggested that autism and ADHD each have their own unique 'fingerprint' of executive function deficits and that further research should focus on outlining these profiles (Ozonoff & Jensen, 1999).

Geurts conducted one of the most comprehensive studies to map distinct profiles of EF in ASD and ADHD. The ASD group showed deficits on all EF tasks except interference control and working memory, and significantly greater impairments than the ADHD group on planning and cognitive flexibility. The ADHD group, by contrast, was most impaired on inhibition of prepotent response and verbal fluency (Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2004).

In a study by Booth, the relationship between weak coherence and executive dysfunction was explored. Results showed that ASD group was more detail-focused in their drawings than were either ADHD boys or the controls. Both ASD and ADHD groups showed planning impairments, more severe in the former group. Poor planning did not, however, predict detail-focus (Booth, Charlton, Hughes, & Happe, 2003).

Studies focusing on cognitive profile of individuals with comorbid ADHD and ASD are sparse. Sinzig for the first time investigated specifically the impact of comorbid ADHD in children with HFA on EF performance (Sinzig, Morsch, Bruning, Schmidt, & Lehmkuhl, 2008). Her study replicated previous results reporting impairment of ADHD children in inhibition and working memory tasks and of ASD children in planning and flexibility abilities. The comorbid group showed similarities to the ADHD group with regard to response inhibition but not working memory deficits. She concluded that comorbid ADHD symptoms seem to worsen inhibitory performance in individuals with ASD.

2.2.6.2 Neuroimaging Studies

As mentioned in chap I, there are inconsistencies in both ADHD and ASD neuroimaging literature that make it difficult to determine the similarities and differences between the two disorders.

One of the consistent findings is that frontostriatal regions are implicated in both disorders. Functionally, both disorders experience disruption to both resting and active brain networks, although this disruption requires further clarification in each disorder. Given these variable data, the utility of neuroimaging in the diagnosis of comorbidity presently remains somewhat limited (Gargaro, et al., 2011).

2.2.6.3 Genetic studies

Genetic research strategies could be very useful in the study of comorbidity in child psychiatry.

Both autism and ADHD are known to be highly heritable conditions (Bailey, et al., 1995; Levy, et al., 1997), and individual differences in autistic traits and ADHD traits in the general population are highly heritable (Constantino, Przybeck, Friesen, & Todd, 2000; Constantino & Todd, 2003; Ronald et al., 2006; Ronald, Happe, & Plomin, 2005). Genetic linkage findings report that similar areas of the genome might be involved for autism and ADHD (Smalley et al., 2002).

Behavioural genetic analysis of both autism and ADHD has been carried out by Ronald et al. (2008) to determine the degree of phenotypic and aetiological overlap between autistic traits and ADHD behaviours in the general population. 6,771 families with twins born in 1994–6 participated in their study when the twins were 8 years old. Parents completed the Childhood Asperger Syndrome Test and the Conners' DSM-IV subscales. They also collected teacher data for a sub-sample.

They reported significant correlations between autistic and ADHD traits in the general population (.54 for parent data, .51 for teacher data). They also found a moderate degree of overlap in genetic influences on autistic and ADHD traits, both throughout the general population and at the quantitative extreme. There was also substantial overlap in suspected cases (41% of children who met criteria for an ASD had suspected ADHD; 22% with suspected ADHD met criteria for an ASD). The authors concluded that there are some common genetic influences operating across autistic traits and ADHD behaviours throughout normal variation and at the extreme (Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008).

The limited available evidence also indicates that to a large extent shared genetic risk factors underpin the co-morbidity between ASD and ADHD as well as the correlation in traits. Constantine in a twin study, using an epidemiological sample of 219 male twin pairs aged 7–15

years, reported that variation in attention problems explained a significant proportion of variation in autistic traits (Constantino & Todd, 2003).

2.2.7 Treatment Strategies for ASD and ADHD

The investigation of comorbidity is an important issue in the clinic, as accurate diagnosis is the first step towards effective treatment. The use of psychotherapeutic medication such as the ones which are effectively used for treatment of the ADHD symptoms, been investigated for treating inattention, impulsivity, and overactivity in children with autism.

Handen in a double-blind placebo-controlled study of Methylphenidate (MPH) in children with autism and symptoms of ADHD showed that MPH effectively decreases the scores by 50% on the Conners scale without affecting scores on the Childhood Autism Rating Scale (CARS) (Handen, Johnson, & Lubetsky, 2000). In another study by Santosh (2006), it was found that children with autism and ADHD can respond to stimulant medication equally as well as children with pure ADHD (Santosh, Baird, Pityaratstian, Tavare, & Gringras, 2006).

Despite these promising findings, treatment of ADHD symptoms in individuals with autism should be carefully considered as there are some reports showing that individuals with autism are more susceptible to more severe adverse side effects of stimulant medications (Handen, et al., 2000; Santosh, et al., 2006).

2.3 Conclusion

In summary, clinical judgment and mounting research findings from genetic, neuropsychological and neuroimaging studies suggests that comorbidity between ADHD and ASD is a real and frequent occurrence.

However, due to the prevention of comorbid diagnoses by the major international classification systems, the comorbidity of ADHD and ASD has not been acknowledged until recently and as a result studies focusing on individuals with ADHD and ASD are sparse, so the manifestations of comorbid form is not entirely clear. Moreover, there was a trend in previous studies to exclude children with comorbid neurodevelopmental disorders to enable them to study the pure picture of the disorders that has led to a gap in our knowledge of cognitive profile of the comorbid cases.

Therefore, in this study, a group of children and adolescents with a clinical diagnosis of comorbid ASD and ADHD was included to assess their clinical manifestation and cognitive profile in order to investigate whether the cognitive profile of comorbid cases is more similar to either ADHD or ASD group or is a mixed pattern of deficits to a certain extent.

Examinations of such similarities and differences at the cognitive level would therefore support the notion that children with comorbid ASD-ADHD are the same to or different from pure groups not only on a clinical level but also on a neuropsychological level.

Understanding the comorbidity better would then allow for not only more accurate diagnoses but also more effective treatment of children with autism and ADHD.

Chapter 3

Methodology

3.1 Chapter Overview

The aim of this chapter is to describe the general methodology of the study and the sample recruitment, and to outline the research design, data collection and methods of analyses. Specific details of the methodology, analyses, and results for each task included will be described in the relevant chapters (Chapter 5 to Chapter 7).

3.2 Participant Recruitment and Inclusion/Exclusion Criteria

The study was approved by the Wandsworth Research Ethics Committee (approval number: 08/H0803/161). Research and Development approval was also obtained to allow for recruiting from Primary Care Trusts (R&D Reference RDLSL 454). Written informed consent was obtained from the parent or guardian of every participant.

3.2.1 Recruitment of Clinical Groups

Participants in the clinical groups were recruited from the Child and Adolescent Mental Health Services (CAMHS) and Primary Care Trust (PCT) in South London and Maudsley (SLaM) and outpatient neurodevelopmental clinics, based in Croydon, Southwark, Lambeth and Lewisham as well as from selected child development centres/clinics in these boroughs. These services are community clinics and are considered as secondary referral clinics. Each of the boroughs provides comprehensive child & adolescent mental health services to the residents within the borough. Therefore, the cases attending these clinics were representative of an inner-city population.

The inclusion and exclusion criteria were sent to the psychologists working as the Biomedical Research Council (BRC) coordinators in the clinics with a request for their help in recruitment. The coordinators identified individuals with clinical diagnoses of ASD, combined-type ADHD or comorbid ASD-ADHD who met study inclusion/exclusion criteria. Once potential cases were identified, they were invited to take part in the study. If, after receiving all of the information, families agreed to take part they were contacted via phone to arrange a visit and to obtain consent before testing commenced. Some of the participants were recruited through attending parent support groups in the above mentioned boroughs. In addition, an advertisement was placed on the National Autistic Society (NAS) website. The proportion of cases from different sources is presented in Chapter 4, Table 4-1.

3.2.1.1 Inclusion Criteria

Individuals with a clinical diagnosis of high functioning autism (HFA), Asperger's disorder and/or a diagnosis of combined type ADHD/hyperkinetic disorder (HKD) were invited to take part in the study.

The participants were required to be male, between the ages of 7 and 16 years, and high functioning (IQ above 70).

Only males were recruited in the study as both ADHD and ASD disorders have a gender bias and are more common in boys than girls; thus, in terms of practicality, it was much easier to recruit suitable number of boys. Including only males also eliminated the possible gender related confounds since previous studies have shown that gender has an effect on cognitive task performance, although the findings are not consistent. For example, in a study on response inhibition and hyperactivity conducted in preschoolers, Berlin and Bohlin (2002) found boys to show a lower level of inhibitory control than girls (Berlin & Bohlin, 2002). Comparable results were obtained by Carlson and Moses (2001), who found 3- and 4-year-old girls to significantly outperform boys on measures of inhibitory control (Carlson & Moses, 2001). Seidman et al (2005) studied a group of ADHD boys and girls aged from 9 to 17 years, and were unable to confirm a gender difference. In their study, girls and boys with ADHD were significantly more impaired in some measures of EF than healthy comparisons, but did not differ significantly from each other. They suggested that executive dysfunctions are correlates of ADHD regardless of gender and age, at least through the late teen years (Seidman et al., 2005).

Only high functioning individuals were included as the cognitive tests were only suitable for normally intelligent individuals.

3.2.1.2 Exclusion Criteria

To reduce the number of confounding factors, certain exclusion criteria were applied. Children were excluded from the study for any of the following reasons:

- If English was not their native/main language
- If they suffered from certain medical disorders like Fragile X, or if they had a past history of severe traumatic brain injury, or a diagnosis of epilepsy as this may affect cognitive functioning.
- If they had other comorbidities such as Major Mood Disorder, severe Obsessive Compulsive Disorders (OCD), Psychosis, Conduct Disorder, or Tourette Syndrome.
- If they were on any psychotropic medication except for stimulants in ADHD
- Cases with substance abuse

In the clinical group, having a diagnosis of comorbid Oppositional Defiant Disorder (ODD) was permitted, but comorbid Conduct Disorder (CD) was an exclusion criterion. This was based on a study by Faraone (1995) which suggested that ADHD associated with CD is perhaps a distinct subtype, but this did not appear to be the case for ADHD associated with ODD (Faraone et al., 1995).

Previous studies have used familial aggregation, longitudinal, and genetic designs to assess whether there are separate or overlapping etiologies for ADHD with ODD or CD from ADHD only and to clarify the patterns of comorbidity found in clinical data.

ODD has been commonly reported in individuals with ADHD. Wood et al. in a twin analysis reported a high overlap between hyperactivity/impulsivity and oppositionality (r=0.95) and a medium overlap between inattentiveness and oppositionality (r=0.56) and suggested that some aspects of the inattentive behaviours being distinct from oppositionality, but the hyperactive/impulsive behaviours being largely indistinguishable from oppositionality. They concluded that the hyperactive/impulsive behaviours of the ADHD phenotype is shared etiologically and phenotypically with oppositional behaviours in the general population (Wood, Rijsdijk, Asherson, & Kuntsi, 2009).

There is an ongoing debate on whether ADHD with and without CD are distinct disorders. Family studies suggest that ADHD with CD represents a specific subtype of disorder with familial risk factors independent of ADHD alone and that ADHD with CD might be a distinct genetic subtype of ADHD (Faraone et al., 1995; Faraone, Biederman, Keenan, & Tsuang, 1991; Faraone et al., 2001; Stewart, DeBlois, & Cummings, 1980). Hurtig et al. (2007) reported that ADHD adolescents with comorbid CD exhibited more severe symptoms of ADHD than those without CD (Hurtig et al., 2007).

Taking the previous studies into consideration, we decided to exclude the individuals with a diagnosis of ADHD-CD in order to study a more homogenous group.

Certain exclusion criteria were set for the eye tracking section as follows:

- Visual acuity of all children was required to be normal or corrected-to-normal (children wearing glasses could keep them on during the experiment).
- No individuals should wear contact lenses.
- They were excluded from the eye movement session if they had a history of serious eye problems (such as glaucoma, or cataract), eye surgery (such as strabismus surgery), or other medical condition that may have influenced vision or ocular motor function.
- None of the participants were taking medications known to affect eye movements (e.g. anticonvulsants, sedatives or hypnotics).

3.2.2 Recruitment of a Control Group

Boys without a diagnosis of childhood psychiatric disorders in the same age range as the probands with IQ≥70 were recruited from local primary and secondary schools. The same exclusion criteria for the probands applied for the controls as well. In addition, boys who had a sibling with a diagnosis of ASD and/or ADHD were not included.

Letters and emails were sent to a number of schools in different boroughs including Southwark, Lambeth and Lewisham asking for their help in recruitment. The flyers were put on notice boards, and invitation letters and information sheets were distributed to the male students who met the inclusion criteria in the classroom. Posters and flyers were also put in local leisure centres like libraries and sport clubs.

3.2.3 Recruitment of Siblings

A group of full siblings of the closest age to the probands with no diagnosis of childhood psychiatric disorders was targeted to test whether the biomarkers represent an endophenotype, and whether there is evidence for correlations between the liabilities to the familialities of autistic and ADHD traits. Siblings were required to be male with IQ≥70. The same exclusion criteria for the probands applied to the siblings as well.

3.3 Diagnostic Measures and Classification of Cases in Research Groups

Participants were all evaluated using screening questionnaires, i.e. Conners rating scale and Social Communication Questionnaire (SCQ). SCQ and Conners were administered to all participants to screen for ASD and ADHD symptomatology, and to assess the phenotypic behaviours. Parents were also asked to complete the Strengths and Difficulties Questionnaire (SDQ), and the appropriate modules on the Development and Well Being Assessment (DAWBA) online. Here, a brief description of the questionnaires will be presented.

The **Social Communication Questionnaire** (Rutter & Bailey, 2003) is a 40-item parent-report questionnaire about characteristic autistic behaviours, for example: '*Has he/she ever seemed to be more interested in parts of a toy or an object (e.g. spinning the wheels of a car) rather than using the object as it was intended*'. Each item is scored 0 or 1, with 1 being the score for an endorsement of each symptom of autism. Total scores can range from 0 to 39 (the first item is a language screening question that is not included in the total score). Nineteen items rate current behaviour and 20 rate behaviour when the child was 4–5 years old. The cut-off score for autistic-spectrum disorder is ≥15.

The SCQ was first developed in response to the need for a reliable and valid screening instrument. It was based on the items from the autism diagnostic interview – revised (ADI-R)

(Lord, Rutter, & Le Couteur, 1994) which has established validity for a diagnosis of autism (Berument, Rutter, Lord, Pickles, & Bailey, 1999). SCQ was designed as companion measure to ADI-R, parent/caregiver dimensional measure of ASD symptomatology, and is appropriate for children of older than fours years.

Charman et al. in 2007 collected SCQ from 119 children between 9 and 13 years of age with special educational needs with and without ASD (the Special Needs and Autism Project, SNAP) and found that SCQ showed strong discrimination between ASD and non-ASD cases with a sensitivity of 0.85, and a specificity of 0.75 (Charman et al., 2007).

The distribution of SCQ score reported by Chandler and Charman in 2007 (Chandler et al., 2007) are consistent with the notion that the SCQ represents a dimensional measure of autistic symptomatology in the population. Thus, although the SCQ has not previously been used as a quantitative measure of autistic symptomatology in the way that the Social responsiveness Scale (SRS) (Constantino et al., 2004) has been, the adoption of the SCQ as a dimensional score in the study is conceptually justified and supported by findings from Chandler and Charman (Chandler, et al., 2007).

Like the SRS, the SCQ ask parents to indicate whether a range of autistic symptoms are present or have ever been present. SCQ differs from SRS in that the extent of the symptoms is not quantified. For example, in the SCQ, parents rate symptoms as present or absent, whereas in the SRS, they have to decide on the extent of symptoms (each item is scored from 0 ('never true') to 3 ('almost always true')). The SCQ also differs with respect to the inclusion of the items concerned with the presence of behaviour at any point in development. Arguably, the use of a measure that includes items concerned with both current and past behaviours may better reflect the severity of the disorder.

Similar to SRS, higher score on SCQ is correlated with greater number of autistic traits. SCQ has been shown to be highly correlated with ASD symptoms severity as measured by the ADI-R (total algorithm score: r=.79, p<.001) and consensus ICD-10 symptom count (r=.71, p<.001), although more moderately correlated with ADOS total algorithm score (r=.42, p<.001) (Chandler, et al., 2007).

Taken all into consideration, it was decided to use SCQ as a dimensional score in quantitative chapter (Chapter 8).

The **Conners 3rd Edition-Parent Report Short Version (Conners-3P);** (Conners, 2008) was used to screen the participants for ADHD characteristics, i.e. inattention, hyperactivity and impulsivity. The version used in this study is a 43-item that sets a new standard for assessing ADHD and related learning, behaviour, and emotional problems in children and adolescents. It contains the 18 hyperactive–impulsive and inattentive DSM-IV symptom subscales. The parent

indicates on a four-point scale how well each attribute describes the child: not true at all (0), just a little true (1), pretty much true (2), very much true (3). Items include, for example, *'is always on the go'* or *'acts as if driven by a motor'* and *'has difficulty sustaining attention in tasks or play activities'*.

Based on the parent's coding, Conners transforms raw scores into age and gender standardized t-scores. The cut-off score for inattention and hyperactivity/impulsivity T scores is ≥60.

The **Strengths and Difficulties Questionnaire (SDQ)** (Goodman, 1999) is a brief questionnaire to assess positive and negative behaviours in children and adolescents. The parent version was used in this study and has 25 items that can be rated as being not true (0), somewhat true (1), or certainly true (2). Five subtests, each consisting of five items are included. Four of the five subtests assess difficulties including conduct problems, hyperactivity/inattention, emotional problems, and peer problems. They are added together to make a difficulty score ranging from 0-40. The fifth subtest is the prosocial subset and assesses the positive aspects of behaviour and reflects the individual's strengths. Table 3-1 shows the cut-off score on SDQ.

The SDQ has been shown to be a useful tool to help the detection of child psychiatric disorders. In a study by Iizuka et al. (2010), it was shown that SDQ ratings were different in a group of individuals with HFA from those with ADHD. In the parent rating, HFA children had significantly higher scores in the subscales of emotional symptoms and peer problems, and they concluded that subscales may reflect behavioural, emotional, and social characteristics of HFA and ADHD (Iizuka et al., 2010).

Table 3-1: The Cut-off score for SDQ

Parent SDQ Total Score	**Borderline (14-16)**	**Abnormal (17-40)**
Emotional symptoms Score	4	5-10
Hyperactivity Score	6	7-10
Conduct Problems Score	3	4-10
Peer Problems Score	3	4-10
Prosocial Behaviour Score	5	0-4

The **Development and Well Being Assessment (DAWBA)** (Goodman & Ford, 2000) is a package of questionnaires, interviews, and rating techniques designed to generate ICD-10 and DSM-IV psychiatric diagnoses on 5-16 year-olds. It covers several disorders in detail: separation anxiety, specific and social phobias, post-traumatic stress disorder, OCD, generalised anxiety, major depression, hyperkinesis/ADHD, ASD, Tic disorder, ODD, and conduct disorder. Selected modules from DAWBA relevant to ASD and ADHD and common comorbidities were administered for the purposes of this study.

Parents were asked to complete a structured interview on the DAWBA website (www.dawba.net) about psychiatric symptoms and their resultant impact. For those who had difficulty accessing the webpage, a trained researcher assisted them. Parents could also describe the problems in their own words. In the presence of positive symptoms in any domain, parents were asked additional questions about the impact of these problems on the child's life. The information provided by parents was then brought together by a computerised diagnostic algorithm that predicts likely diagnoses according to ICD-10 and DSM-IV separately.

In the study by Goodman (2000), DAWBA showed excellent discrimination between community and clinic samples in rates of diagnosed disorder. It showed a minimum estimate of 89% specificity in the community sample and 92% sensitivity in the clinic sample (Goodman & Ford, 2000).

Diagnostic Tools: To ensure that patient participants met appropriate diagnostic criteria, the Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS) were used for Autism. ADHD/hyperkinetic syndrome diagnosis was confirmed using the Parent Account of Childhood Symptoms (PACS) diagnostic.

3.3.1 ASD Assessment

The **ADI-R** (Lord, Rutter, & Le Couteur, 1994) is a 93-item standardized, semistructured interview for parents of autistic individuals with autism, which provides a diagnostic algorithm for the ICD-10 and DSM-IV definition of autism. It consists of five sections: opening questions; questions on communication (both early and current); those on social development and play (both early and current); questions about repetitive and restricted behaviours (all scored for both current and ever judgments); and some questions concerning general behaviour problems.

In ADI-R there are questions about the age when abnormalities were first manifested, and if there was any loss of skills and progressive deterioration in order to provide accurate information for differential diagnosis between autism and syndromes such as Rett's disorder or disintegrative disorders.

The ADI-R was administered to those who had a clinical diagnosis of pure autism and in comorbid cases as well as in those with pure ADHD who scored ≥15 on SCQ.

Scoring was made on the basis of the interviewer's judgment of the code that best fits the behaviours described by the parents. Most ADI-R items can be coded from 0 to 3: *no definite behaviour of the type specified (0); behaviour of the type specified probably present but defining criteria not fully met (1); and definite abnormal behaviour of the type described in the definition and coding (2),* with a code of *3 used to indicate extreme severity.*

Each ADI-R item is scored for current behaviour, with the exception of a few items where the behaviour is relevant only during particular age periods. For example, reciprocal friendship and circumscribed interests are coded only for those above 10 years of age.

The ADI-R algorithm is generated by selection of ADI-R items that most closely depicted the specific abnormalities described in DSM-IV and ICD-10. The cut-off scores are 8 on communication domain, a minimum score of 10 on social domain, and 3 for restricted and repetitive behaviours.

The **ADOS** (Lord et al., 2000) is a semistructured, standardized observation of social interaction, communication, play, and imaginative use of materials for individuals suspected of having ASD. The ADOS was first introduced in the 1980s proposed as a complementary instrument to ADI. The observational schedule consists of four 30-45 minute modules, each designed to be administered to different individuals according to their level of expressive language and development, ranging from those with no expressive language to verbally fluent children and adults.

ADOS has been shown to be effective in categorizing children who definitely have autism or not, but has had lower specificity and sometimes sensitivity for distinctions involving children with milder form of ASDs (Lord, et al., 2000) (Bishop & Norbury, 2002).

In the original normative sample for Modules 1–3, the ADOS generally achieved 94% correct classification. The exceptions were the ASD versus Non-spectrum Module 2 specificity of 87% and Module 3 sensitivity of 90% (Lord & Rutter, 1999).

As in the current study, the participants were all high functioning with a good verbal ability and above the age of 7, ADOS-module 3 was administered to those who had a clinical diagnosis of pure autism and in comorbid cases as well as in those with pure ADHD who scored ≥15 on SCQ. Module 3 provides 13 activities and 28 ratings. ADOS items are scored on a 4-point scale, from 0 to 3.

To receive an ADOS classification of Autism or ASD, an individual's scores must meet separate cut offs in a Communication domain (*Autism spectrum* cut-off ≥2, and *Autism* cut-off ≥3), a Social domain (*Autism spectrum* cut-off ≥4, and *Autism* cut-off ≥6), and a summation of the two (*Autism spectrum* cut-off ≥7, and *Autism* cut-off ≥10) based on the original algorithm. In the original algorithm, restricted and repetitive behaviours are coded but they are not counted in the diagnostic algorithm.

The new algorithm for ADOS classification was then introduced by Gotham et al. (Gotham, Risi, Pickles, & Lord, 2007). They suggested taking into account restricted, repetitive behaviour items in the diagnostic algorithm. In addition, they proposed to merge the existing social and communication domains to one domain called 'Social affect score'. The revised algorithm has

been shown to increase comparability between modules and improve the predictive validity of the ADOS for autism cases compared to the original algorithms (Gotham et al., 2008).

In this study, the revised algorithm was used in which the final ADOS score was defined as the summation of Social Affect and Restricted and Repetitive Behaviour (*Autism spectrum* cut-off ≥7, and *Autism* cut-off ≥9).

3.3.2 ADHD Assessment

PACS: The diagnosis of ADHD according to DSM-IV-criteria in probands was based on the Parental Account of Childhood Symptoms (PACS), which is a semistructured, standardized, investigator based interview, assessing ADHD with a good inter-rater reliability as well as predictive and discriminative validity (Taylor & Schachar, 1986). PACS was first developed as an instrument to assess children's behaviour problems as seen at home. It was undertaken by a trained interviewer. PACS has previously been used in a number of epidemiological, genetic and interventional studies (Taylor & Sandberg, 1991).

The sections of PACS used in this study included inattentive behaviour and hyperactivity & impulsivity. Parents were asked not for their ratings of problems, but for detailed descriptions of what their child had done in specified situations over the previous weeks while he was not on medication. Such situations were defined either by external events (e.g., watching television, reading a book or comic, playing alone, playing with friends, travelling, family outings, shopping trips, parental report of school problems) or by behaviours shown (e.g., crying, worries, tempers, fighting with siblings). Then the ratings were made by the interviewer, on a four-point scale of severity (0 to 3) and frequency in the previous week. The judgments of frequency and severity were made independently and according to written criteria. Scores on frequency and severity were then averaged to yield the score for each item. In our sample, most of the individuals with ADHD were on regular medication for their ADHD symptoms. This meant that to administer PACS, interviewer had to focus on the times the individual was off medication (like during weekend for some individuals, or on evenings when beneficial effects of medication is small). Inevitably, this might lead to reduction in symptoms endorsement in those cases.

PACS was administered in those who had a clinical diagnosis of pure ADHD, in comorbid cases, and in those with ASD who scored ≥60 on Conners. An algorithm was used to derive each of the DSM-IV ADHD symptoms from the PACS interview data. The diagnosis of ADHD was made if sufficient number of items was identified to fulfil DSM-IV criteria, and impairment (based on the severity of symptoms identified in the PACS interview) was present (Chen, et al., 2008). The cut-off score in PACS was set at 6 in either domain of inattention or hyperactivity.

3.3.3 Classification of Cases in Research Groups

Following the research assessment, all the data were reviewed and cases were allocated to different groups on the basis of their scores in the diagnostic assessments from different sources of informants, including parents, interviewer's judgment and observation, and for some individuals teacher Conners at the time of diagnosis also has been obtained from the medical records.

To confirm the ASD diagnosis, ADI-R/and or ADOS score above the cut off was necessary. The algorithm cut offs for ADI-R and ADOS have been developed for research diagnosis of ASD. The threshold has been modified for various research studies by allowing scores to fall one point below threshold on one behavioural domain of the ADI-R to ascribe a diagnosis of ASD. Thus modified criteria adopted for this study based on the AGRE study (International Molecular Genetic Study of Autism Consortium, 1998).

If the participants with a clinical diagnosis of pure autism scored high on Conners, then PACS was administered. If they scored above the cut-off on either domain of PACS ($\geq$ 6 on either inattention or hyperactivity), then they were allocated to the comorbid group.

If the participant with a clinical diagnosis of pure ADHD scored high on SCQ, then ADI-R and ADOS were administered. If they scored above the cut-off they, were allocated to the comorbid group.

3.3.4 Control Group

Typically developing boys who showed a willingness to take part in the study were assessed by the screening questionnaires, SCQ and Conners. All of the controls were required to have an SCQ score<15. If they scored high on Conners, then PACS was administered.

3.3.5 Siblings

15 full siblings with no diagnosis of ASD, ADHD or a comorbid ASD-ADHD agreed to take part in the study. Siblings of probands were assessed by the screening questionnaires, SCQ and Conners.

3.4 Test Battery

Following a literature review of existing measures, the tasks which had already been validated by showing case-control differences for ADHD and ASD in previous studies were selected. New tasks were designed to fill gaps identified in existing research.

The battery included a series of neurocognitive measures consisting of Executive Function measures (including Go/No-Go and antisaccade tasks) and a prosaccade task; Theory of Mind measures (including Triangle Task and Strange stories) and a Cueing task; and Central Coherence measures (including Embedded Figures Task, Sentence Completion, and Block

Design). A thorough literature review and further theoretical details of the cognitive tasks will be given in the relevant chapters (Chapter 5 to Chapter 7).

As the emerging evidence shows the utility of eye tracking in the evaluation of cognitive profiles, it was decided to design novel experimental tasks based on the modification of already validated eye movement tasks assessing visual attention in order to look for putative attentional and cognitive biomarkers. Various paradigms have been used to investigate eye movements in children with psychiatric disorders. Given that the major impairments of autistic children lie in social skills and communication, it was decided to design a cueing task to assess the effect of social and non-social cues in saccadic eye movements. In addition, as response inhibition is one of the difficulties children with ADHD show, it was decided to include an antisaccade task which is a suitable test to investigate whether oculomotor inhibition is indeed affected in ADHD.

An Eye Tracker (the SR Research Eyelink 1000) was used to track the eye movements during a set of tasks (antisaccade/prosaccade and cueing task) to examine the basic characteristics and cognitive modulation of eye movements in each group. No study has compared ADHD and ASD children on eye movement measures. Moreover, there is no study exploring the eye movement patterns in a group of children with a comorbid ASD-ADHD diagnosis.

Before moving to the next section, it is important to mention how recording eye movements can be of use as a research tool.

The study of eye movement is a source of valuable information to both researchers and clinicians. Over the past decades, eye movements have been applied as an experimental tool to provide insight into many different disorders (Klein & Ettinger, 2008).

3.4.1 Why do people study eye movements?

To scientists, the eye is a rich source of information about perceptual, cognitive and affective processes. Consequently, eye movements have been studied in a wide variety of contexts including research into various psychological processes, such as visual perception and visual attention. Eye movements are readily accessible to observation and systematic examination (Leigh & Zee, 2006).

The fovea is the part of the retina that is specialised for high-acuity vision and optimal processing of colour and shape. Most detailed processing of a visual stimulus is, therefore, achieved by retaining its image within about 0.5º of the centre of the fovea. Stimulation of retinal neurons (rod and cone cells) by light waves causes the transmission of neural signals down the optic nerves via the lateral geniculate body of the thalamus to the primary visual area of the occipital lobe, resulting in the experience of vision (Leigh & Zee, 2006).

One purpose of eye movements is to enable high-acuity vision by compensating for head movements. As accurate visual perception is only possible when images on the retina are stable, most processing of visual information takes place when the eye fixates on a stimulus. Eye movements fall into several categories. Leigh and Zee classified them on the basis of their functions into vestibular, visual fixation, optokinetic, smooth pursuit, nystagmus quick phase, saccades and vengeance eye movements. These eye movements can be summarised further into two broad functional categories, *gaze-shifting* (those that bring an image onto the fovea) and *gaze-stabilising* (those that retain an image on the fovea) eye movements.

Saccades that are of interests to the current study are rapid eye movements used to move the high acuity fovea of the retina to visual targets for detailed visual analysis, and can be divided into two broad classes: *reflexive, sensory-triggered movements* which are made in response to the sudden appearance of a novel visual stimulus; and *volitional movements* which are elective saccades made as part of purposeful behaviour. Detailed information on saccadic eye movements will be given in Chapter 5.

3.4.2 Why Study Eye Movements in Child Neuropsychiatric Disorders?

There is a growing body of literature investigating eye movements in children with psychiatric disorders. Making an eye movement is an important way of exploring the environment. Therefore, eye movements provide us with some information on how children experience their daily environment and may increase our knowledge about the various complex behavioural processes underlying psychiatric disorders (Rommelse, Van der Stigchel, & Sergeant, 2008).

Recording eye movements has several benefits over standard procedures: First, relative to reaction time (RT) data, they provide a much richer data set which allows for better understanding of the underlying neurophysiological mechanisms. Eye movements can also provide valuable information regarding the metrics and dynamics of oculomotor control, such as velocity, duration and trajectories of saccades.

Second, it is quite easy to record eye movements with high spatial and temporal resolution. Eye-trackers provide data about the timing as well as the accuracy of responses (Luna, 2007). Non-invasive techniques enable eye movement systems to be easily applied in children. Also, eye movement tasks are generally very simple and not difficult to perform by children with psychiatric disabilities. The paradigms require no advanced cognitive skills such as language, reading, or complex motor responding, and are relatively straightforward and easy to explain to participants even at an early age (Rommelse, Van der Stigchel, & Sergeant, 2008). The latter is especially important for the current study as there are reports of motor coordination problems in both ADHD and ASD (Murray, 2010).

Various paradigms have been used to investigate eye movements in children with psychiatric disorders. For the aims of this study, saccadic eye movements were explored in order to assess the specificity and overlap of saccadic abnormalities across ADHD and ASD. A thorough literature review on the eye movement tasks employed in this study will be given in the relevant chapters (Chapter 5 and Chapter 6).

3.4.3 Procedure

Due to test demands, participants were given the option to spread the assessment over two separate sessions, each taking approximately three hours or to carry out testing in one day with a lunch break. Participants were advised to take breaks when needed and were informed they could discontinue testing at any time.

The ones who were on stimulants were asked to stop taking it 48 hours before the testing session. All participants were tested individually in a quiet room with minimal distractions.

The order of administration for all measures in the task battery is presented in Appendix B. For the purpose of the current study, only selected tasks embedded in a larger test battery are reported. The order was maintained when the testing was split into two sessions. Tasks alternated between pencil-and-paper and computer-administered, as well as between visual and verbal modalities, in order to provide variety. Some exceptions occurred to the set order when extra time became available or when participants were slower on certain tasks than anticipated. Positive comments were made throughout the sessions to encourage participants, but no feedback was given about the correctness of responses during the test phase of a task.

If the participants had the clinical diagnosis of ASD or comorbid ASD-ADHD or they were pure ADHD with a high score on SCQ, then ADOS assessment were administered first. Then, intellectual functioning of each individual was assessed through the administration of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1997) on all the 4 subtests including vocabulary; block design, similarities, and matrix reasoning. Then the test battery was administered in a fixed order for all the individuals.

3.5 Statistical Analyses

The Statistical Package for Social Science, version 15.0 for Windows (SPSS, Inc., Chicago, Illinois) was used to analyse the data presented in this thesis. Analyses were conducted with and without outliers (data points exceeding 3 SD above/below group means) and if no difference occurred, outliers remained.

Where possible, parametric tests were used to enable robust assessment that allowed for investigation of possible interaction effects. Wherever the data did not fulfil the assumptions necessary for analyses using parametric statistics, appropriate transformations were applied or

non-parametric statistical tests were used (Kruskal-Wallis Test χ^2, Mann-Whitney *U*, Fisher's Exact Test, Spearman's r_s as appropriate).

Means and standard deviations (SD) of the outcome variables were reported throughout the thesis. For the main findings, the confidence intervals (CI) of the variables of interest were also reported (Please find the reported CIs in Appendix G).

Levene's test of equality of variance was performed to examine homogeneity of variance. The Greenhouse-Geisser correction was used to adjust for sphericity violations where necessary.

3.5.1 Significance Level

The *p* values<.05 were considered and reported as significant; however, for the value of interests where there was an a priori hypothesis, *p* values<.1 were presented as a non-significant trend and discussed if a medium to large effect size of the difference was observed.

3.5.2 Analyses strategy for each chapter

Different analyses were carried out in different chapters according to outcome variable, based on the hypotheses for each chapter. The details are as follows:

1) Case-Control comparisons in Chapter 5 to Chapter 7. These three experimental chapters adopted a categorical approach with aim to assess whether ASD and ADHD could be discriminated based on their neuropsychological profiles and to explore the pattern of response in the comorbid group. As the comparisons were made between more than two groups, analysis of variance (ANOVA) with groups (ADHD, ASD, comorbid, and control) as the independent variable and task performance measures as the dependent variables were carried out. Partial eta-squared effect sizes (η^2) were provided.

Some protection against Type I error was provided by the use of ANOVA in analyses. LSD post -hoc was employed to examine a between-group difference; which makes no attempt to control the Type I error and does not control for the family-wise error.

As this study is one of the only studies which has explored cognitive markers for ASD, ADHD, and a comorbid group, it was considered best to present findings uncorrected for multiple testing so that future research can further test the cognitive traits that may represent markers. Therefore, an alpha adjustment (Bonferroni correction for multiple comparisons) has not been applied systematically throughout the thesis in order to avoid Type-II errors.

In addition to Partial eta-squared (η^2), effect sizes of pairwise comparisons were also calculated according to the formula

$$d = \frac{\bar{x}_1 - \bar{x}_2}{s},$$

where x_1=mean of group 1, x_2=mean of group 2 and S (SD pooled)=pooled standard deviation of the two groups (Cohen, 1988). The pooled standard deviation was calculated as follows:

$$s = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2}},$$

where n_1 is the sample size of Group A with its SD; and n_2 is the sample size of Group B with its SD.

If a medium or large effect size was observed, then the power analysis was carried out in order to test if the current sample had enough power to detect group differences.

2) Quantitative analyses in Chapter 8. In order to further investigate the predictive accuracy of ASD and ADHD traits for the tasks performance, separate backward stepwise multiple regressions were conducted. Autistic symptoms (e.g. SCQ scores), ADHD symptoms (e.g. Conners scores), FSIQ and age were included in the analyses.

Stepwise regression was chosen over hierarchical method as in hierarchical regression, the predictors are selected based on previous work, while in the current study the analyses were exploratory.

The reason to choose backward stepwise regression over forward stepwise regression was that the forward method runs a higher risk of making a Type II error (i.e. missing a predictor that doe in fact predict the outcome).

Critical F values were specified to control entry and removal of effects from the model. Stepping method criteria was set at entry: .05 and removal: .10. For all analysis, the critical value for model entry needed to exceed the critical value for removal for the model. A maximum number of steps were not specified.

Analyses were conducted using backward regression models where analysis began with a full model (all independent variables in the model) and variables are eliminated in an iterative process. At each step after step 0, the removal statistic is computed for each effect eligible to be removed form the model. After the elimination of each variable the fit of the model was tested. If no value had an effect on the removal statistic that was less than the critical value for removal from the model, stepping is terminated. This enabled separate regression analyses to identify the variables that significantly contributed to emotion labelling and discrimination performance.

3) Looking for putative endophenotype in Chapter 9 where selected tasks from the current study which showed case-control differences were chosen as potential endophenotypes. The main test of shared familial risk (a key criterion for an endophenotype) between a cognitive performance measure and clinical phenotype is a significant difference in cognitive performance

between siblings of affected probands and controls (Andreou, et al., 2007). Therefore, data obtained from siblings were compared to the control group using independent t-tests.

In case a significant sibling-control difference was observed, probands were also entered in the comparison in order to see whether the mean performance of siblings lie between probands and controls.

3.5.3 Correlations

All correlations were conducted using Pearson or Spearman (in case of violations of parametric assumptions) correlations. Where there was a directional hypothesis, a one-tailed test was chosen; otherwise a two-tailed test was selected. Fisher's *r*-to-*z* transformation was used to test whether the correlations differed between diagnostic groups.

3.5.4 Controlling/Testing the effect of age and IQ

Throughout the thesis, the effect of age and IQ was both controlled for and tested for in each experiment:

- The effect of age and IQ on the task performance was evaluated by conducting correlation between age/IQ and the task variable both across the groups and within each group (*testing for the age and IQ effect*). This was done in order to evaluate the developmental changes in each task and to assess whether the task performance can be partly explained by IQ.
- In addition, the effect of age and IQ were statistically *controlled for* where appropriate. Group differences were reported both with and without adjustment for age/IQ to ensure that the genuine group differences were not confounded by the effect of age and IQ. Given the wide age range and small sample sizes, even though there were no group differences for age, all the analyses were carried out with and without covarying for age. Moreover, as the groups were not matched for IQ, analysis was conducted both with and without IQ as a covariate. However, there is a debate on the issue of using IQ as a covariate in analyses in psychopathology research (Miller & Chapman, 2001). For example, Miller argued that IQ would be very likely to be meaningfully related to brain damage, so using IQ as a covariate would disrupt any comparison of brain-damaged and control groups' performance as it is part of the group differences. Similarly, in schizophrenia research, given the great amount of literature on cognitive deficits in schizophrenia, variables such as IQ that have been viewed as confounds may be incorporated into the picture of the disorder. Therefore, IQ need not be viewed as something to control for, but rather as a feature of the disorder (Miller & Chapman, 2001).

This view is also valid in ADHD and ASD research. It has been found that the symptoms of ADHD and lower IQ covary in children and 100% of the association between ADHD diagnosis and IQ has been shown to be accounted for by genetic influences that are shared by ADHD and IQ (Kuntsi et al., 2004). This finding suggests that the cognitive deficits in ADHD might be part of the disorder and controlling for the effect of IQ would therefore hide any genuine group difference. Similarly uneven IQ profile may be phenotypically linked with ASD (Nishiyama et al., 2009); thereby removing the effects of IQ may remove some of the effects of group differences attributed to having a diagnosis of ASD.

Chapter 4

Sample Characteristics

4.1 Clinical Groups

Of the 232 suitable families approached from the clinic, 104 families agreed to participate, reflecting a participation rate of about 44.8%. Of those 104 individuals, 47 had a clinical diagnosis of combined type ADHD/ hyperkinetic disorder, 36 had a clinical diagnosis of ASD, and 21 had a clinical diagnosis of comorbid ASD-ADHD.

In total, 8 individuals were excluded from the study; 7 individuals with a clinical diagnosis of ADHD and 1 child with ASD. There were various reasons for these exclusions. For example, amongst ADHD cases, parents of one child refused to complete the diagnostic tools, so there was not enough information to confirm the diagnosis. One of the ADHD participants scored high on SCQ, so based on the algorithm for the study, an administration of ADI-R and ADOS was necessary, but as the family was not available for further assessments, we had to exclude the individual from the study. For three participants, the validity of children and parents' data was under query. One individual was excluded as his full scale IQ was 68, and he did therefore not meet the study criteria. Finally, one participant had a diagnosis of conduct disorder in his medical records. The individual with ASD was excluded as he was non-compliant and unable to follow the instructions given by the experimenter due to severe autism. So in total, 96 participants were retained for further analysis and investigation: 40 with a clinical diagnosis of combined type ADHD/hyperkinetic disorder, 35 with a clinical diagnosis of ASD, and 21 with comorbid ASD-ADHD.

A summary table with numbers and diagnosis of referrals from each source is presented in Table 4-1. A detailed table including age, diagnosis, and source of referral is presented in Appendix C. From the whole sample (N=96), 91 individuals (94.8%) were recruited from the outpatient clinics including CAMHS (N=89) and PCT (N=2); and only 5 individuals (5.2%) were recruited from other sources (NAS website). The reason that only 2 of the participants were recruited from the PCT clinics is that there was no BRC coordinator working at the PCT to help and therefore, the researchers had to directly liaise with the consultant paediatricians to recruit the cases which due to their professional engagement and time limitations, this was not found easy.

Following the research assessment, all the data were reviewed and cases were allocated to different groups on the basis of their scores on the diagnostic assessments from different sources of informants, parents, interviewer's judgment and observation, and for some individual

Conners Teacher Questionnaire at the time of diagnosis was also obtained from the medical records.

Table 4-1: Sampling sources in summary

		Sources of Recruitment					
		Outpatient clinics				Website	Total
		Lambeth	Lewisham	Southwark	Croydon		
Clinical Diagnosis	ADHD	1(2.5%)	11(27.5%)	10(25%)	17(42.5%)	1(2.5%)	40
	ASD	3(8.6%)	13(37.1%)	2(5.7%)	14(40%)	3(8.6%)	35
	Comorbid	2(9.5%)	12(57.1%)	1(4.8%)	5(23.8%)	1(4.8%)	21
Total		6(6.25%)	36(37.5%)	13(13.54%)	36(37.5%)	5(5.21%)	96

As mentioned in methods section 3.3.2., to confirm an ADHD diagnosis, a score ≥ 6 on either domain of PACS (≥6 on either inattention or hyperactivity) was required. Two of our ADHD cases did not meet full PACS criteria as they scored 5 on either or both domains. However, they were included in the ADHD group because they had a clinical diagnosis of ADHD, were impaired, and had been on medication for several years. Accordingly, we consider these cases to represent either residual ADHD or cases with partial responses to treatment. For these two individuals, we requested Conners Teacher Questionnaire in order to support the diagnosis and in both cases the T-Score was above the cut-off.

All of the individuals who had a clinical diagnosis of comorbid ADHD-ASD from clinic except two, met both ASD and ADHD criteria as described above. One of them met the criteria for ASD, but he scored 1 on each PACS domain. Therefore, he was allocated to the pure ASD group. The other one scored 4 and 5 on PACS inattention and hyperactivity, respectively; however, his teacher Conners was positive and he has been on medication for several years, so he was retained in the comorbid group.

Administration of the diagnostic tools as mentioned in the methods section enabled us to clarify the research diagnosis and to categorise individuals in different groups based on our research criteria: 35 individuals in the ADHD group, 19 individuals in pure ASD group, and 42 in comorbid group. Overall, 17 cases with a clinical diagnosis of ASD were then reassigned to the comorbid group, whereas only 5 cases with a clinical diagnosis of ADHD were re-classified into the comorbid group. As the figure shows, the number of comorbid cases based on research criteria doubled the number which had been diagnosed by the clinic.

The high number of re-allocations of ASD cases to the comorbid group may reflect the fact that diagnostic criteria preclude the diagnosis of ADHD in the presence of ASD on the basis of the fact that the symptoms characteristic of ADHD disorders are within the symptomatology of autism. However one should be careful in interpreting these data, because the sample was selected from a clinic population, and they may not fully represent the pattern of comorbidity from population derived samples.

Table 4-2: Groups allocation in summary

		Research Diagnosis			
		ADHD	**ASD**	**Comorbid**	**Total**
Clinical Diagnosis	**ADHD**	35	0	5	40
	ASD	0	18	17	35
	Comorbid	0	1	20	21
Total		35	19	42	96

4.2 Control Group

From the large number of letters sent out, only 50 families showed willingness to hear more about the study, and of those, only 25 individuals participated. All of the controls had an SCQ score <15. However, 14 of them scored above the cut-off on either domain or both domains on Conners. PACS was then administered to this group to explore the ADHD symptomatology in more depth. One individual who met the PACS criteria was then excluded from the study. Finally, 24 healthy controls were retained and assessed to investigate case-control differences.

4.3 Siblings

15 full male siblings with IQ ≥ 70 were assessed. None had a clinical diagnosis of ADHD or ASD. These samples are derived from siblings across the entire proband dataset including 6 siblings from the comorbid group, 4 from the ASD group, and 5 from the ADHD group.

4.4 Participants

In total, 135 boys were assessed in this study in five subgroups including 35 individuals with a research diagnosis of ADHD, 19 individuals with a research diagnosis of ASD, 42 in the comorbid group, 24 controls and 15 siblings. All participants were aged between 7 and 16 years and had a full-scale IQ (FSIQ) ≥70 as assessed by the Wechsler Intelligence Scale for Children. This chapter presents characteristics of the three clinical groups and the control group. Sibling data will be presented separately in Chapter 9.

4.4.1 Demographics

Table 4-3 presents demographic information by group. An analysis of variance (ANOVA) with age as the dependent variable and group as the between-subjects factor showed no significant differences in age among the groups (p>.05). ANOVA was conducted on the IQ scales (FSIQ, PIQ, and VIQ) with group as the between-subjects factor. Significant differences were found for FSIQ, PIQ, and VIQ (all p<.05).

Further analysis showed that the two groups of children with ADHD symptomatology (i.e. pure ADHD and comorbid groups) had significantly lower FSIQ, PIQ, and VIQ compared to controls (LSD post-hoc tests for ADHD-control comparisons: p<.001 for FSIQ, PIQ, and VIQ and for comorbid-control comparisons: p<.001 for FSIQ, p=.008 for PIQ, and p=.001 for VIQ), whereas the ASD group did not differ from controls on FSIQ, PIQ, or VIQ (all p>.05). The ASD group had a significantly higher FSIQ relative to the ADHD group (p=.04). No significant difference was observed between the ASD and comorbid group in FSIQ (p>.05) and no significant differences amongst the clinical groups were observed for PIQ, and VIQ (all p>.05).

Figure 4-1 depicts the association between age and FSIQ in the present sample. A negative correlation was found for age and FSIQ (r=-.24, p=.008), PIQ (r=-.17, p=.07), and VIQ (r=-.24, p=.008) indicating the higher cognitive ability in younger individuals across the group. The same pattern of correlation was also observed in each group. Age and FSIQ correlations were as follows in each group: control group (r=-.22, p=.30), ASD group (r=-.04, p=.88), ADHD group (r=-.25, p=.15), and comorbid group (r=-.37, p=.02).

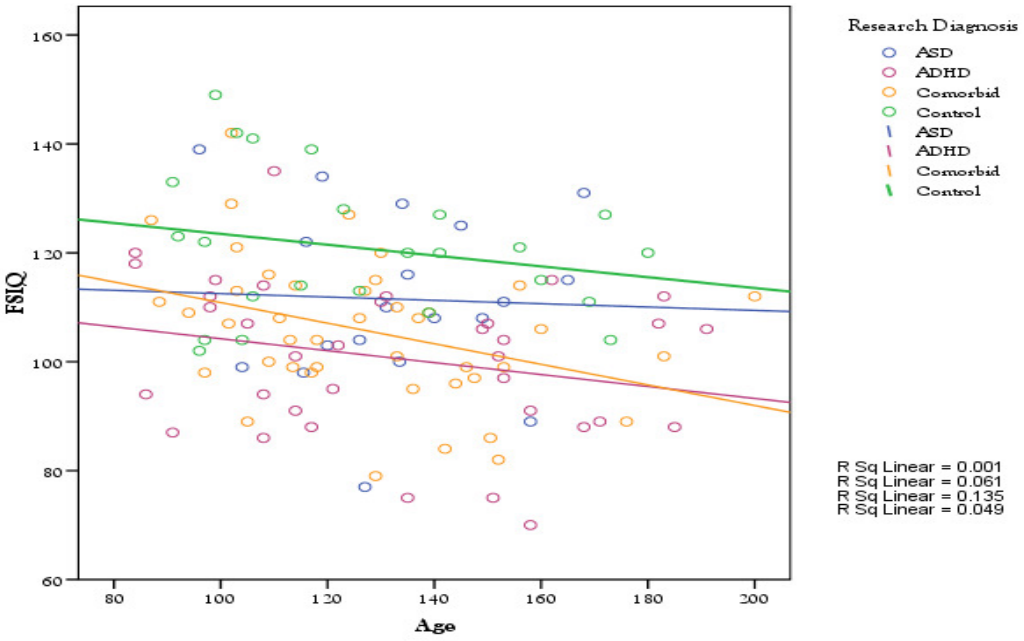


Figure 4-1: Association between age and FSIQ by group

Table 4-3: Descriptive characteristics of the sample: Means (SD), [Range]

	ASD (N=19)	**ADHD (N=35)**	**Comorbid (N=42)**	**Controls (N=24)**	**$F_{(3,1116)}$**	**P**	**Post-hoc LSD**
Age in month	133.42(19.70)	132.26 (31.88)	127.58 (25.51)	126.58 (29.16)	.40	.75	
[Range]	[96-168]	[84-191]	[87-200]	[91-180]			
FSIQ	111.47 (15.98)	100.69 (14.16)	105.64 (13.14)	120.83 (13.06)	10.84	<.001	Controls> ADHD, Comorbid*
[Range]	[77-139]	[70-135]	[79-142]	[102-149]			ASD>ADHD*
PIQ	108.05 (14.54)	99.00 (13.85)	104.19 (13.22)	115.46 (12.50)	7.44	<.001	Controls> ADHD, Comorbid*
[Range]	[80-136]	[64-131]	[75-141]	[100-141]			
VIQ	112.47 (18.47)	102.34 (15.89)	105.79 (14.57)	121.71 (15.39)	8.15	<.001	Controls> ADHD, Comorbid*
[Range]	[78-145]	[75-133]	[77-146]	[93-151]			

**Post-hoc test, p<.05*

4.4.2 Behavioural Profile of the Sample

All of the clinical measures except for Conners inattention and Conners hyperactivity/impulsivity were normally distributed. The latter scores were severely skewed due to a ceiling effect in ADHD and comorbid groups and none of the transformation formulas were able to normalise them. Therefore non-parametric statistical tests were used for the Conners scores. Figure 4-2 depicts behavioural profile by group and Table 4-4 shows descriptive statistics for each group based on their behavioural profile.

As expected, the clinical groups were rated as significantly more impaired than the control group on almost all indices from the SDQ, SCQ, and Conners. On the SCQ, which measures autistic behaviours, comorbid and ASD groups did not show significantly different scores. They scored significantly higher than the ADHD and controls (LSD post-hoc tests, $p<.001$). Also, relative to controls, children with ADHD had a significantly higher score in SCQ (LSD post-hoc tests, $p<.001$).

For the Conners questionnaire, ratings were significantly higher in the two group with ADHD (i.e. pure group and comorbid group) relative to ASD and controls (Post-hoc Mann–Whitney U $p<.001$). Individuals with ASD did not differ from the control group on Conners hyperactivity ($p>.05$); however they scored higher than controls on inattention (Post-hoc Mann–Whitney U $p=.01$) (Table 4-5).

The SDQ suggested greater overall impairment in the comorbid group, followed by ADHD and then ASD group relative to controls. Ratings for emotional problems, peer problems, and prosocial subscale were strikingly similar in the two pure groups ($p>.05$). Moreover, comorbid and ASD groups did not show significant differences in emotional problems and prosocial subscale ($p>.05$). However, the comorbid group was significantly more impaired than the ADHD group on these subscales (LSD post-hoc tests, $p=.007$ for emotional problems, and $p=.006$ for peer problems, and $p=.01$ for prosocial domain), and was more impaired than the ASD group on peer problems (LSD post-hoc tests, $p=.04$).

Relative to controls, children with ADHD were more impaired by emotional problems (LSD post-hoc tests, $p=.03$), peer problems (LSD post-hoc tests, $p<.001$), and prosocial domains (LSD post-hoc tests, $p=.006$) (Table 4-4).

In the SDQ conduct and hyperactivity subscales, ratings were similar for ADHD and comorbid groups ($p>.05$). Both groups were significantly more impaired than the controls and the ASD group (LSD post-hoc tests, $p<.001$) on the conduct and hyperactivity subscales. Individuals with pure ASD were not impaired relative to controls on these measures ($p>.05$).

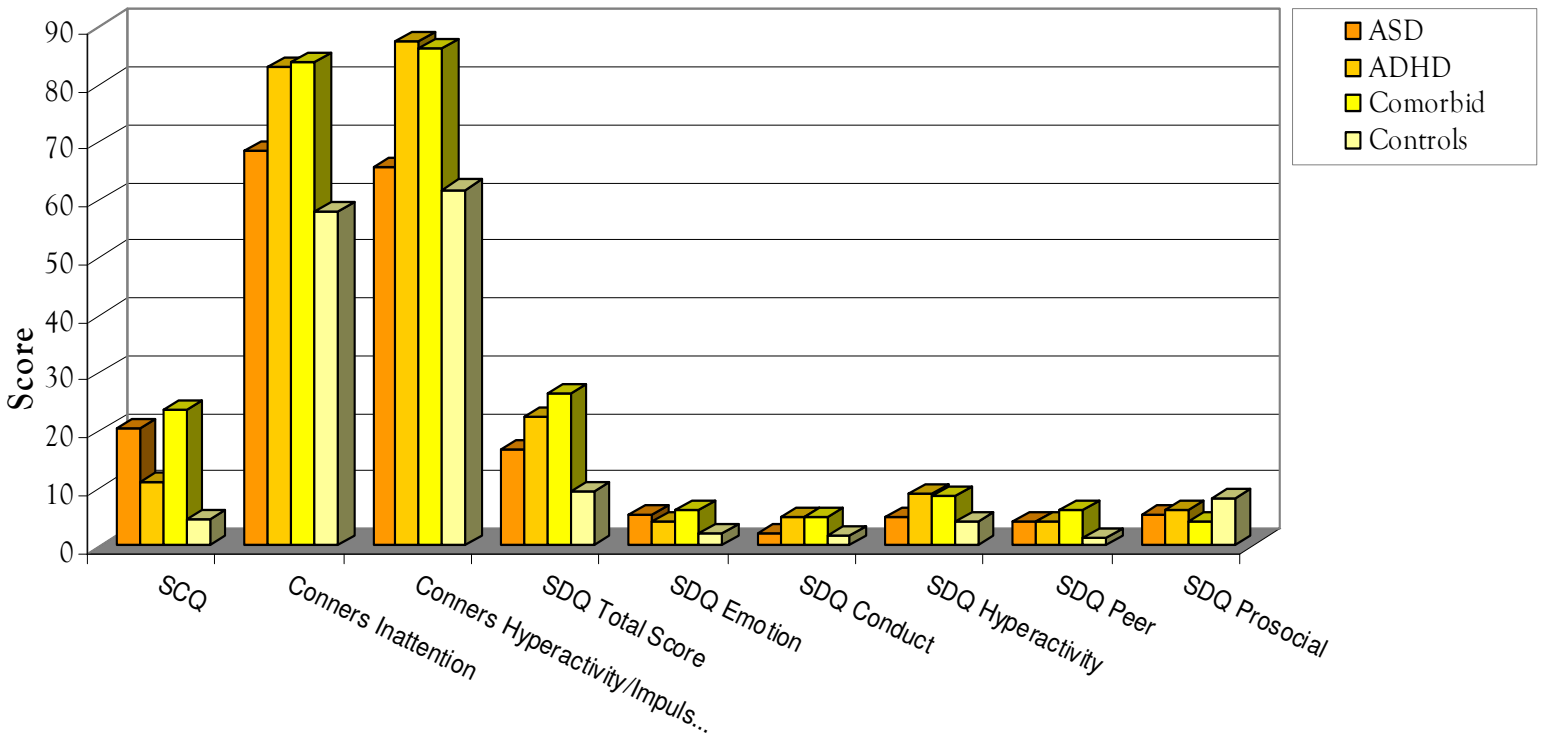


Figure 4-2: Behavioural profile of the sample by group

Table 4-4: Behavioural profile of the sample: Means (SD)

	ASD (N=19)	ADHD (N=35)	Comorbid (N=42)	Controls (N=24)	F	*p*	Post-hoc LSD
SCQ	20.26 (8.15)	11.15 (5.42)	23.43 (5.17)	4.43 (3.84)	69.21	<.001	Comorbid, ASD>ADHD*>Controls*
SDQ Total Score	16.79 (5.42)	22.41 (5.65)	26.36 (4.35)	9.47 (5.32)	38.66	<.001	Comorbid>ADHD*>ASD*>Controls*
SDQ Emotion	5.43 (2.03)	4.17 (2.69)	6.36 (2.56)	2.00 (2.14)	11.12	<.001	Comorbid>ADHD*>Controls* ASD>Controls *,
SDQ Conduct	2.07 (2.23)	4.93 (1.60)	5.04 (2.57)	1.87 (1.88)	13.12	<.001	Comorbid, ADHD>ASD*,Controls*
SDQ Hyperactivity	4.93 (2.50)	9.00 (1.31)	8.75 (1.53)	4.13 (2.80)	33.57	<.001	Comorbid, ADHD>ASD*,Controls*
SDQ Peer	4.36 (1.65)	4.31 (2.69)	6.21 (1.99)	1.47 (1.51)	16.10	<.001	Comorbid>ADHD*,ASD*>Controls*
SDQ Prosocial	5.29 (1.90)	6.03 (2.28)	4.29 (2.00)	8.27 (1.87)	12.58	<001	Controls>ADHD*,ASD*>Comorbid*

**Post-hoc test, p <.05*

Table 4-5: Conner's T-Score: Means (SD)

	ASD (N=19)	ADHD (N=35)	Comorbid (N=42)	Controls (N=24)	Kruskal–Wallis χ^2	P value	Post- hoc Mann–Whitney U
Conners Inattention+	68.26(15.37)	82.85(7.53)	83.67(7.12)	57.83(11.51)	52.00	<.001	Comorbid, ADHD>ASD*,Controls**, ASD>Controls**
Conners Hyperactivity/ Impulsivity+	65.47(15.05)	87.56(4.04)	86.33(6.64)	61.79(17.55)	53.91	<.001	Comorbid, ADHD>ASD*,Controls*

+ Nonparametric analyses conducted (Kruskal–Wallis $\chi 2$ and post-hoc Mann–Whitney U reported).

Only the combined subtype of ADHD was recruited from the clinics for the purpose of this study. However, considering the PACS inattention and hyperactivity scores, then showed that ADHD and comorbid groups can be further classified in 3 different subgroups: combined, predominantly inattentive, and predominantly hyperactive. Moreover, as explained earlier in total 3 individuals classified in a group with residual ADHD symptoms as their PACS score were below the cut-off (Table 4-6).

Table 4-6: ADHD subtypes in ADHD and comorbid groups based on PACS assessment

ADHD Subtype / Research Diagnosis	Combined subtype	Inattentive subtype	Hyperactive subtype	Residual	Total
ADHD	16	12	5	2	35
Comorbid	21	16	4	1	42
Total	37 (48.05%)	28 (36.36%)	9 (11.69%)	3 (3.90%)	77

Figure 4-3 depicts the distribution of ADHD symptomatology as was assessed by PACS. The proportion of different subtypes was not significantly different between the two groups with ADHD (*Fisher's exact*=1.2, p=0.8), and similar distribution of subtype was observed across the two groups. Looking in more depth at ADHD symptoms of pure ADHD and comorbid groups did not show any differences on their inattention/hyperactivity profile, and no differences between the two groups were detected on PACS inattention (p>.05), and PACS hyperactivity (p>.05). Moreover, in both groups PACS inattention score was higher than PACS hyperactivity score, i.e. symptoms of inattention were more pronounced than hyperactivity.

In the present sample, 64.7% of individuals with a research diagnosis of ADHD (N=22) were on regular medication (Methylphenidate) for their ADHD symptoms, compared with only 31.7% of individuals with a research diagnosis of comorbid ASD-ADHD (N=13). However, as mentioned in section 3.4.3, the ones who were on medication were asked to stop taking it 48 hours before the testing session.

Figure 4-4 and Figure 4-5 show distribution of autism symptomatology as was assessed by ADOS and ADI-R; respectively. Comparing the autism profile of the ASD and comorbid groups also did not demonstrate any significant differences using an independent samples t-test (p>.05 for all ADI-R and ADOS domains).

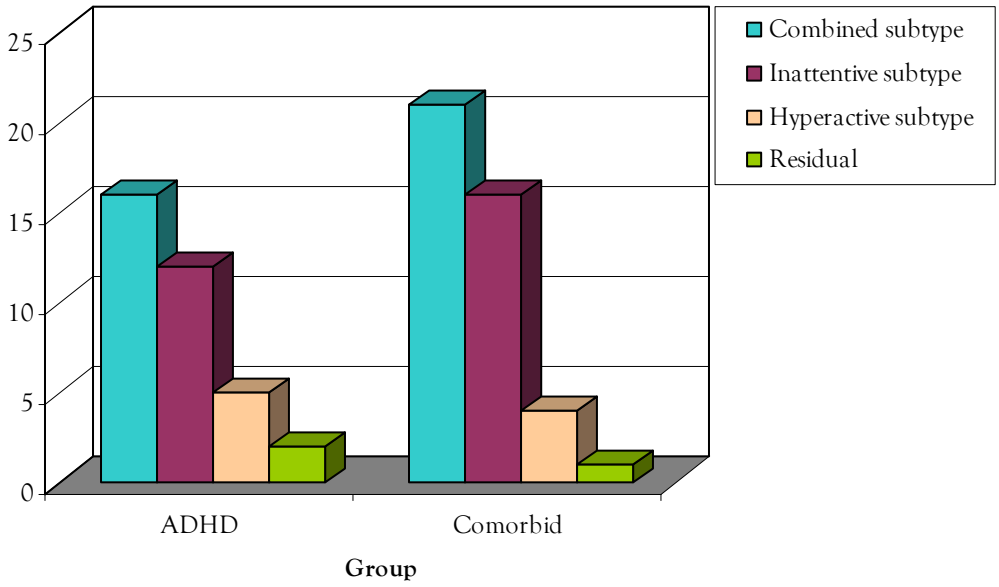


Figure 4-3: ADHD Subtypes in ADHD and Comorbid Groups based on PACS Assessment

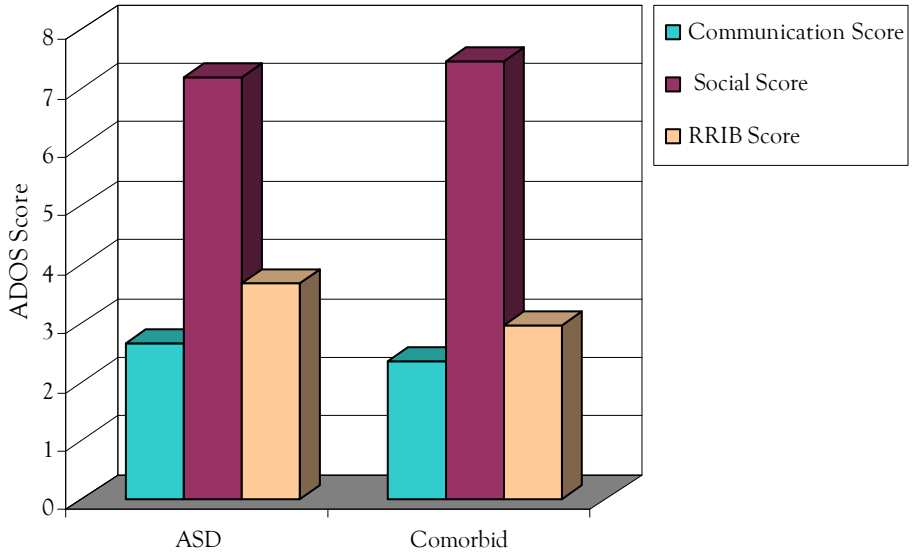


Figure 4-4: Autism Symptoms in ASD and Comorbid Groups based on the ADOS Score

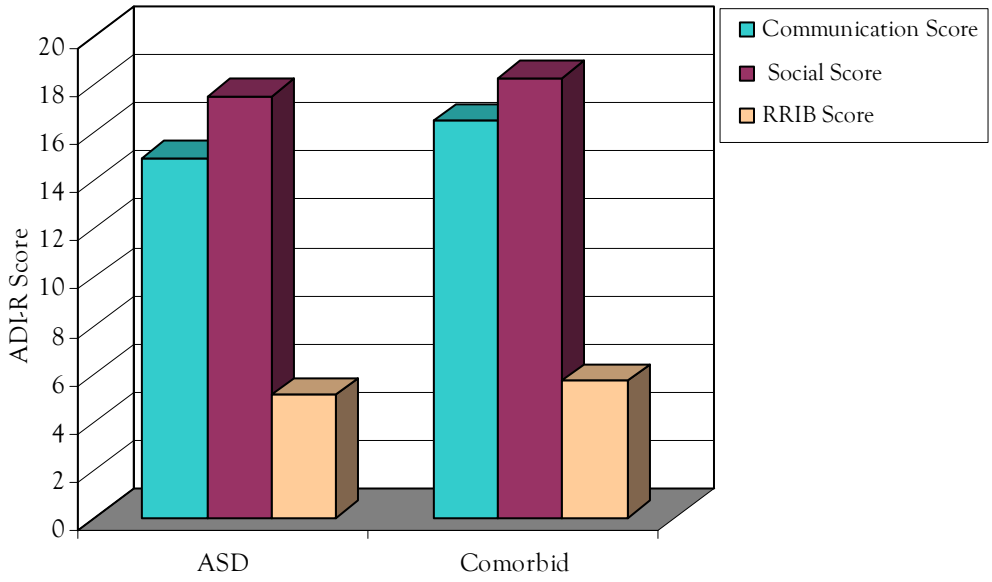


Figure 4-5: Autism Symptoms in ASD and Comorbid Groups based on the ADI-R Score

4.4.3 Age and IQ Effect on Clinical Measures

Table 4-7 shows the correlation between age and IQ with clinical measures as were rated on SDQ, SCQ, and Conners. No developmental changes were observed for the clinical measures, across the groups.

However, FSIQ was mildly correlated with SCQ (r=-.21, p=.02) and SDQ total score (r=-.25, p=.02). Moreover, the FSIQ was moderately correlated with Conners inattention score (r_s=-.41, p<.001) and Conners hyperactivity score (r_s=-.33, p<.001).

4.4.4 Correlation between Clinical Measures

Table 4-8 shows the correlation between the clinical measures across all groups. Spearman's rank correlation (ϱ) is reported for the associations with Conners inattention or hyperactivity/impulsivity scores and Pearson correlation (r) is reported for the rest of associations.

In ASD and comorbid groups, Pearson correlation showed a significant correlation between SCQ measure and ADI social and communication domains (r=.67, p<.001 and r=.52, p<.001; respectively). There was no significant correlation between any of the clinical measures with RRIB (p>.05).

As was expected based on the fact that social and communication impairments are often seen as almost indistinguishable in real life and have been suggested to result from a single cognitive

deficit, social score as measured by ADOS and ADI-R separately, was highly correlated with communication score (r=.60, p<.001 for ADOS and r=.65, p<.001 for ADI), whereas both social impairments and communication difficulties were only mildly correlated with restricted/repetitive interests and behaviours (RRIB) as measured both by ADOS and ADI-R. The correlations were only significant for RRIB and ADI social score (r=.27, p=.04) and RRIB and ADI communication score (r=.30, p=.03).

In both groups with ASD (i.e. pure ASD and comorbid group), there were no significant correlation between Conners scores and ADI/ADOS variables (p>.05) i.e. ADHD symptoms were not associated with autistic behaviours as measured by ADI-R or ADOS.

In ADHD and comorbid groups, Conners inattention score was only mildly correlated with PACS inattention score (r_s=.28, p=.01) and Conners hyperactivity score was moderately correlated with PACS hyperactivity (r_s=.33, p=.004).

Table 4-7: Correlation between age and IQ with clinical measures

	SCQ	Conners Inattention	Conners Hyperactivity	SDQ Total Score	SDQ Emotion	SDQ Conduct	SDQ Hyperactivity	SDQ Peer	SDQ Prosocial
Age	.04	-.07	.05	-.02	-.004	-.04	-.10	.08	.03
FSIQ	-.21*	-.41**	-.33**	-.25*	-.03	-.20	-.32**	-.16	-.10

** Correlation is significant at the 0.05 level,* *** Correlation is significant at the 0.01 level.*

Table 4-8: Correlation between clinical measures

	Conners Inattention	Conners Hyperactivity/ Impulsivity	SDQ Total Score	SDQ Emotion	SDQ Conduct	SDQ Hyperactivity	SDQ Peer	SDQ Prosocial
SCQ	.41*	.33**	.58**	.58**	.20	.29**	.57**	-.58**
Conners Inattention		.60**	. 50**	.22*	.46**	.64**	.25*	-.17
Conners Hyperactivity/Impulsivity			.52**	.20	.49**	.66**	.25*	-.14
SDQ Total Score				.68**	.72**	.73**	.78**	-.46**
SDQ Emotion					.20	.23*	.50**	-.34**
SDQ Conduct						.52*	.41**	-.31**
SDQ Hyperactivity							.36**	-.23*
SDQ Peer								-.45**

** Correlation is significant at the 0.05 level,* *** Correlation is significant at the 0.01 level.*

4.5 Chapter Summary

Following the recruitment for the clinical groups, 96 participants were retained in the study for further analysis and investigation: 40 with a clinical diagnosis of combined type ADHD/hyperkinetic disorder, 35 with a clinical diagnosis of ASD, and 21 with comorbid ASD-ADHD. The participants were further allocated in different groups based on the research criteria: overall, 17 individuals with a clinical diagnosis of ASD were reassigned to comorbid group, whereas only 5 individuals with a clinical diagnosis of ADHD were classified as the comorbid group.

The allocation of ASD cases to comorbid group may reflect the fact that diagnostic criteria preclude the diagnosis of ADHD precludes the diagnosis of ADHD if there is a diagnosis of ASD on the basis of the fact that the symptoms characteristic of ADHD disorders are of the symptomatology of autism. However, one should be careful in interpreting these data, because the sample was selected from a clinic population, and they may not fully represent the pattern of comorbidity from population derived samples.

In addition to the participants with a clinical diagnosis, a group of 15 full siblings with no clinical diagnosis of ADHD or ASD and a control group were included.

In summary, 135 boys were assessed in this study in five subgroups including 19 individuals with a research diagnosis of ASD, 35 individuals with a research diagnosis of ADHD, 42 in comorbid group (as the figures shows, the number of comorbid cases based on research criteria doubled the number of the clinic diagnosis), 24 controls and 15 siblings. All participants were aged between 7 and 16 years and had a Full-Scale IQ (FSIQ) ≥ 70.

In this chapter, the characteristics of the three clinical groups and the control group presents were presented. It was revealed that groups were age-matched, but the IQ score was lower in the two groups with ADHD relative to controls.

Across the groups and also within each group, a negative correlation was found for age and FSIQ indicating the higher cognitive ability in younger group. This finding, most likely reflect a sampling bias rather than age effects on IQ as it was also observed in the control group.

As expected based on previous studies, having a comorbid ADHD-ASD diagnosis seems to worsen the behavioural profile as measured by SDQ which is reflecting the severity and complexity of the comorbid group.

Chapter 5

Executive Function Account & Attentional Abnormalities

5.1 Chapter Overview

As reviewed in Chapter 1, one of the most influential cognitive accounts of both ADHD and ASD is that the behavioural difficulties may arise from 'executive function' (EF) deficits (Barkley, 1997, 1998; Pennington & Ozonoff, 1996), but with the pattern of dysfunction differing in each disorder. Ozonoff and Jensen (1999) suggested that ASD and ADHD each have their own unique 'fingerprint' of EF deficits and that further research should focus on outlining these profiles (Ozonoff & Jensen, 1999). In this chapter, first the definition of EF, and then the relevant studies on executive dysfunction accounts of ADHD and ASD will be addressed. Attentional abnormalities and related studies will then be briefly reviewed. Subsequently, the measures used in the current study to assess EF ability and attention and the findings from this part of the study will be discussed.

5.2 Executive Function

The term 'executive function' (EF) refers to complex cognitive processes underlying the controlled goal directed responses to novel or difficult situations. These higher-order processes include functions such as planning and strategy formation, response initiation and selection, monitoring of responses and action, cognitive flexibility, impulse control, and inhibition of a prepotent response (Hill, 2004; Shallice & Burgess, 1991).

Executive function impairments are typically seen following changes in prefrontal cortex functioning as a result of acquired abnormalities such as brain lesions, infections and brain injury (Stuss et al., 1983; Tucha, Smely, Preier, & Lange, 2000). However, such impairments are also exhibited in neurodevelopmental disorders that are associated with frontostriatal dysfunction, including ADHD, ASD, OCD, Tourette's syndrome, phenylketonuria, and schizophrenia (Ozonoff & Jensen, 1999; Pennington & Ozonoff, 1996; Sergeant, et al., 2002).

ADHD and ASD have quite different clinical presentations, and their core diagnostic criteria do not overlap; yet, both groups show substantial EF deficits. A major limitation to the explanatory power of executive dysfunction accounts is lack of specificity. One response to this problem is to note that EF is an umbrella term that covers a set of dissociable processes. Considering distinct domains within EF might clarify the nature of the deficits in ASD and ADHD, and help us to map out distinct EF deficit profiles both quantitatively and qualitatively.

5.2.1 Executive Dysfunction in ASD

The executive function approach attempts to explain the social and non-social difficulties observed in ASD. For example, the social interaction and communication difficulties have been explained in terms of a lack of cognitive flexibility, such as difficulty in taking another person's perspective (Hill, 2004); rigidity, perseveration and repetitive and stereotyped behaviours have been explained by poverty in the initiation of new non-routine actions or difficulty in set shifting to a new behaviour (Ridley, 1994; Turner, 1999). It has also been suggested that difficulty inhibiting prepotent behaviours may contribute to restricted, repetitive interests and behaviours (Thakkar, et al., 2008).

Studies looking at executive dysfunction in ASD have produced different and somewhat inconsistent results based on the heterogeneity of the samples they used, e.g. in regards to age (children and adolescents or adults), or IQ (high functioning individuals vs. those with lower than average IQ). One of the robust findings in the executive dysfunction domain in children with ASD, which has been replicated in several studies, is impairment in planning (Bennetto, Pennington, & Rogers, 1996; Ozonoff & Jensen, 1999). Impairments in verbal fluency (Ambery, Russell, Perry, Morris, & Murphy, 2006) and cognitive flexibility have also been reported in children (Bennetto, et al., 1996). However, there are also studies which have not replicated executive deficits in ASD. For example, Minshew et al. did not find cognitive flexibility impairments (Minshew, Goldstein, Muenz, & Payton, 1992).

In summary, as Hill summarised from the autism literature (Hill, 2004), impairments most consistently present in at least two key aspects of EF in ASD: planning (as assessed by Tower of Hanoi/London) and flexibility (as tested by Wisconsin Card Sort Test (WCST) and intra/extra-dimensional shift of the ID/ED task).

The neural basis of EF deficits in ASD has been investigated using fMRI. A study of response inhibition by Kana et al. in 2007 in a group of adults with ASD showed decreased anterior cingulate cortex (ACC) activation relative to healthy controls (Kana, Keller, Minshew, & Just, 2007). In addition, they found decreased functional connectivity between the inhibition network (ACC, middle cingulate gyrus, insula) and the right middle and inferior frontal and right inferior parietal regions which suggests an atypical inhibition circuitry in individuals with ASD. Spatial working memory was investigated in a study of adults with ASD and healthy controls by Luna in 2002 (Luna et al., 2002). Decreased task-related activation in the dorsolateral prefrontal cortex (DLPFC) and posterior cingulate cortex (PCC) was seen in the ASD group which suggests that frontostriatal networks are dysfunctional in ASD.

5.2.2 Executive Dysfunction in ADHD

As mentioned in Chapter 1, the core executive dysfunction account was first proposed by Barkley in 1997 and is now one of the commonly noted theories which attempts to explain ADHD at the cognitive level. He argued that the core problem of inhibition causes deficiencies in other executive functions such as working memory, self-regulation, and self-control, which in turn contribute to cognitive motor control problems such as inhibiting inappropriate responses, resisting interference, and executing complex sequences of responses (Barkley, 1997, 1998).

In line with Barkley's model, there are numerous reports of impaired inhibitory control in children with ADHD as measured by Stop task (Oosterlaan, Logan, & Sergeant, 1998; Schachar, Mota, Logan, Tannock, & Klim, 2000) and the Stroop Test (Houghton et al., 1999). Poor response inhibition has also been shown to be a problem in adults with ADHD (Houghton, et al., 1999).

However, other researchers suggest that reducing the executive dysfunction to poor inhibition alone may not comprise the whole cognitive profile since a broader range of areas of EF have been shown to be impaired in ADHD (Geurts, et al., 2004). For example, planning deficits, as measured by the Tower of London/Tower of Hanoi task, have been reported in children with ADHD (Klorman, Brumaghim, Fitzpatrick, Borgstedt, & Strauss, 1994) and more recently in an adult sample (Young, Morris, Toone, & Tyson, 2007).

In a meta-analysis of 83 studies of executive functioning in childhood ADHD by Willcutt et al. (2005), they summarized that the most consistent deficits were in measures of response inhibition, vigilance, working memory, and planning. They showed that weaknesses in EF were significant in both clinic-referred and community samples which were not explained by group differences in intelligence, academic achievement, or symptoms of other disorders. They concluded that moderate effect sizes and lack of universality of EF deficits among individuals with ADHD suggest that EF impairments are neither necessary nor sufficient to cause all cases of ADHD, and that they appear to be only one important component of the complex neuropsychology of ADHD (Willcutt, Doyle, et al., 2005).

However, as for the ASD literature, there are also studies which failed to replicate executive deficits in ADHD, and as Kuntsi and colleagues suggested, impaired cognitive performance in ADHD is not restricted to EF and there is a more general behavioural dysfunction including impairment in attentional alerting, orienting, response preparation, and control (Kuntsi, McLoughlin, et al., 2006).

The neural basis of executive function deficits in ADHD has been explored using fMRI. Some of the task-based fMRI studies focused on inhibitory control as response inhibition is a central feature of impulsivity and is commonly observed in ADHD. In a study by Pliszka (2006), they

used fMRI to study adolescents while they were performing a Stop signal task. Increased activation in ACC during successful inhibition trials was found. However, in contrast to controls, individuals with ADHD failed to activate the ACC and the left ventrolateral prefrontal cortex after unsuccessful inhibition (Pliszka et al., 2006).

Schulz (2004) examined the inhibitory control processes in adolescents with ADHD using fMRI during their performance in a Go/No-Go task and found that individuals with ADHD showed enhanced responses during inhibition in ventrolateral prefrontal cortical areas that subserve response inhibition, as well as in anterior cingulate gyrus (Schulz et al., 2004).

5.2.3 Executive Dysfunction in ASD versus ADHD

There are only a few studies that have directly compared executive functioning in children with a diagnosis of ASD and ADHD in an attempt to identify cognitive deficits that are specific to each disorder. (See (Geurts, et al., 2004; Goldberg et al., 2005; Happe, Booth, Charlton, & Hughes, 2006; Johnson, Robertson, et al., 2007; Ozonoff & Jensen, 1999; Sinzig, et al., 2008)).

The findings of these studies, as will be briefly discussed, differed to some extent. A reason for this might be the differences in the age ranges within the samples and the different types of tasks that were employed.

Goldberg found little difference between ADHD and ASD executive functioning profiles. However, the majority of the above mentioned studies have identified differences between ADHD and ASD groups in several executive domains, particularly regarding planning, flexibility, and response inhibition.

Goldberg and Bougakov explored executive functioning in children with HFA (N=17), ADHD (N=21) and healthy controls (N=32) in the age range of 8-12 years using the CANTAB (Cambridge Cognition, 1996): the Stockings of Cambridge task; the Intra-Dimensional/Extra-Dimensional set-shifting task; and the Spatial Working Memory task (SWM); and only found group differences in spatial working memory, with more severe impairment in the HFA group (Goldberg & Bougakov, 2005).

Ozonoff and Jensen (1999) found flexibility deficits in children with ASD but not ADHD. They also found further planning problems in ASD, whereas children with ADHD had response inhibition difficulties on the Stroop Test. Within the ASD group, older (but not higher IQ) participants were less impaired on the EF tasks. It was concluded that there may be age-related improvements in EF in ASD (Ozonoff & Jensen, 1999).

This result was replicated and extended by Geurts et al. (2004). They assessed three groups of children aged between 6 and 12 years (54 ADHD, 41 HFA, and 41 typically developing controls) on a wide range of tasks related to five major domains of executive functioning: inhibition, visual working memory, planning, cognitive flexibility, and verbal fluency. Children

with ADHD exhibited impairments in response inhibition and also in verbal fluency. The HFA group showed deficits in all EF domains, except interference control and working memory, and they had more difficulties than the ADHD group with planning on the Tower of London (ToL) task and cognitive flexibility as measured by WCST. They concluded EF difficulties were more generalized and profound in HFA than the ADHD group (Geurts, et al., 2004).

In another study by Happé et al. (2006), a group of age- and IQ- matched children and adolescents (aged 8-16 years) consisting of ADHD (N=30, mean FSIQ=99.1), ASD (N=30, mean FSIQ=99.1), and controls (N=32, mean FSIQ=106.8) were compared. They found that ADHD children had comparatively greater inhibitory problems on a Go/No-Go task, while the ASD group was significantly worse on response selection/monitoring in a cognitive estimates task, but they did not replicate group differences in flexibility. Also, contrary to Geurts' study, their findings suggested less severe and persistent EF deficits in ASD (including Asperger's disorder) than in ADHD (Happe, et al., 2006). They also considered the developmental trajectory of EF in the two disorders by examining age related changes. They showed that there were clear improvements with age on EF tasks for the ASD group but not for the ADHD group. However, it is not clear whether this developmental progression continues beyond adolescence into adulthood (Happe, et al., 2006).

Johnson et al. has specifically examined sustained attention and response inhibition in ADHD and ASD and, consistent with the pattern identified by previous studies, found that ADHD group was impaired in response inhibition and sustained attention whereas an ASD group did not exhibit sustained attention deficits and showed broadly normal response inhibition (Johnson, Kelly, et al., 2007).

5.2.4 Executive Dysfunction in Comorbid Group

Studies focusing on cognitive profiles of individuals with comorbid ADHD and ASD are sparse. To date, studies assessing EF deficits in both ASD and ADHD have not devoted a great deal of attention to individuals with a dual diagnosis of ADHD and ASD. In the studies by Goldberg et al. and Happé et al., autistic children with ADHD were excluded (Goldberg, et al., 2005; Happe, et al., 2006). Geurts et al. only included autistic children with the inattentive ADHD subtype (Geurts, et al., 2004). A novel investigation by Sinzig showed the specific impact of comorbid ADHD-symptoms in children with HFA on EF performance. They assessed 4 groups of children and adolescents aged 6 to 18 years: with ADHD (N=20); with HFA (N=20); with HFA with comorbid ADHD (N=20); and a typically developing group (N=20) on a battery of EF tasks comprising inhibition, flexibility, working memory and planning tasks. Her study replicated previous results reporting impairment of inhibition and working memory in ADHD group and of planning and flexibility abilities in ASD group. The comorbid group showed similarities to the ADHD group with regard to response inhibition but

not working memory deficits. They concluded that comorbid ADHD symptoms seem to worsen inhibitory performance in individuals with ASD (Sinzig, et al., 2008).

5.3 Go/No-Go Task

The Go/No-Go task has been widely used in studies of response inhibition and has been validated by showing case-control differences for ADHD and ASD (Happe, et al., 2006; Rubia, Smith, & Taylor, 2007). The task demands high-level cognitive functions such as decision making, response selection, and motor response inhibition.

The finding of poor inhibitory performance in individuals with ADHD in the Go/No-Go task has been widely replicated in previous studies (Iaboni, Douglas, & Baker, 1995; Rubia, Smith, & Taylor, 2007; Rubia, Taylor, et al., 2001). Happé et al. (2006) showed a higher number of commission errors and omission errors in their ADHD group compared to the ASD group on the Go/No-Go task (Happe, et al., 2006).

Sustained attention refers to the ability to maintain a stable performance level over time. In attention research, errors of omission (failure to detect the target stimulus) are interpreted as sustained inattention symptoms, whereas commission errors are assumed to reflect a lack of inhibition or impulsivity (Corkum & Siegel, 1993).

On Go/No-Go tasks, greater group differences between ADHD and healthy controls for omission errors would indicate a sustained attention deficit whereas greater group differences for commission errors would indicate a response inhibition deficit. Previous studies found that children with ADHD show decreased accuracy in their task performance, showing more omission and commission errors compared to controls (Kalff, et al., 2005).

5.3.1 Neural Substrates of Go/No-GO Task

Evidence from lesion studies confirmed the involvement of the mesial frontal lobes, especially the supplementary motor area (SMA) and anterior cingulate in the Go/No-Go task (Drewe, 1975; Leimkuhler & Mesulam, 1985; Verfaellie & Heilman, 1987). They also reported the role of dorsolateral, medial prefrontal cortex, and caudate (Okazaki et al., 2004)

In studies using fMRI, several brain areas have been shown to be related to inhibition of a motor response in Go/No-Go task including orbital, inferior, dorsolateral and mesial frontal, temporal and parietal cortices, as well as cerebellum and basal ganglia (Rubia, et al., 1999; Rubia, Schuri, von Cramon, & Poeppel, 1997; Russell et al., 2000).

Rubia et al. (2001) found that selective inhibition in the Go/No-Go task activates a bilateral, but more left hemispheric middle-infero-mesio-frontal and parietal network (Rubia, Russell, et al., 2001).

Moreover, event related fMRIs have shown that focused activation of predominantly right inferior frontal cortex correlated with No-Go activity (Konishi et al., 1999; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998).

5.4 Attentional Abnormalities

Many studies have addressed possible abnormalities in patterns of attention in ADHD and ASD. Although attentional difficulty is one of the prominent accounts trying to explain ADHD behavioural symptoms, it does not appear to be highly specific to children with ADHD, as various other clinical groups, such as children with ASD, conduct disorder, and mood and anxiety disorders also show similar deficits (Pennington & Ozonoff, 1996).

Attention is an important function to consider in comorbid ADHD and ASD since inattention is one of the core symptoms of ADHD (APA, 1994) and attentional problems are described in ASD too (Happe, et al., 2006). The patterns of attention deficit, however, are different: while in ASD the problem is primarily shifting attention, individuals with ADHD have trouble in sustaining attention (Happe, et al., 2006).

Shifts in the direction of attention are closely related to shifts in the direction of gaze and it is generally accepted that eye movements and visual attention processes are closely related; they may be directly connected or share common brain resources (Nobre, Gitelman, Dias, & Mesulam, 2000). There is a growing body of literature investigating eye movements in children with psychiatric disorders (Rommelse, Van der Stigchel, & Sergeant, 2008).

The importance of exploring eye movement in childhood neurodevelopmental disorders and the experiments designed for this PhD study has been discussed in Chapter 3, section 3.4. Here the current literature on saccadic eye movement in ADHD and ASD and then the findings from the prosaccade and antisaccade tasks will be presented.

5.4.1 Studying Saccadic Eye Movement with the Gap/Overlap Paradigm

Saccades are rapid eye movements used to move the high acuity fovea of the retina to visual targets for detailed visual analysis. They can be divided into two broad classes: *reflexive, sensory-triggered movements*; and *volitional movements*. Experiments on the preparation of saccadic eye movements can give insight into certain aspects of visual attention. Normal saccades are usually fast, brief, and accurate, so they do not interfere with vision. There is usually a delay of about 200ms from the stimulus to the enactment of a saccade (Leigh & Zee, 2006).

Initiation of visually triggered saccades involves occipital and parietal cortex and their inputs to the superior colliculus, which then projects to the premotor circuit in the brain stem and cerebellum (Vahedi, et al., 1995). Planning of volitional saccades and suppression of reflexive saccades is under the control of the frontal cortex and basal ganglia, which also project to the superior colliculus and brain stem premotor circuit (Muri, Rivaud, Vermersch, Leger, & Pierrot-

Deseilligny, 1995; Vahedi, et al., 1995). Experiments on the preparation of saccadic eye movements can give insight into certain aspects of visual attention. The time preceding a visually guided saccade, i.e. the saccadic reaction time (SRT), within which attentional mechanisms may come into play, is a good index of the pattern of visual attention (Fischer & Breitmeyer, 1987). The basic idea is that any change in the attentional system requires a certain amount of time which is included in the SRT.

Posner proposed the idea that visual attention acts in three steps: disengagement of attention from its current focus, moving attention to a target, and engagement of the target (Posner & Cohen, 1984). Fischer and Weber (Fischer & Weber, 1993) argued that the state of attention (engaged or disengaged) influences the SRT in regards to a stimulus; therefore, this information may be used to discriminate the two disorders. Supporting evidence is found in the results of studies with the 'gap/overlap paradigm' (O'Driscoll et al., 2005) in which the state of fixation can be manipulated. In the overlap condition, the central fixation point remains illuminated when the target stimulus appears. Hence, both stimuli overlap for a certain duration. In the gap condition, the central fixation point is extinguished before the onset of the cue. The 'gap effect' is defined as the difference in saccadic latencies between the overlap condition and the gap condition. A 200ms gap is typically associated with reduced reaction times in the gap condition when compared with the overlap condition. Also, as shown in previous studies, the gap condition leads to an increase in error rate. Conversely, the overlap task is associated with a prolongation of latency and a reduction in error rate (Fischer & Weber, 1997; McDowell & Clementz, 1997).

Fischer and Weber showed that these latency differences are the result of the different states of attention. In the overlap condition, visual attention is engaged with the initial fixation point when the peripheral target stimulus appears. In the gap condition, attention is already disengaged when the peripheral target appears. Therefore, some preparatory steps of the reflexive saccadic eye movement may take place before the target stimulus actually appears. In other words, an already disengaged attentional system allows for faster saccadic responses, and engaged attention inhibits the saccadic system (Fischer & Weber, 1993).

Deficits in the engagement of visual attention are reflected by a reduced gap effect and faster saccadic responses, whereas deficits in attentional disengagement are likely to be reflected by an increased gap effect and overall slower saccadic responses (van der Geest, Kemner, Camfferman, Verbaten, & van Engeland, 2001). Fischer and Ramsperger (Fischer & Ramsperger, 1984) examined the 'express saccade', which is defined by its extremely short reaction time (80 to 130ms in man). Fischer and Weber reported that engaged visual attention tends to inhibit the express saccade, and disengagement of attention leads to the express

saccade; thus, the express saccade is a useful measure of the state of attention (Fischer & Weber, 1993).

5.4.2 Prosaccade/Antisaccade Tasks: Basic Research Findings

Elicitation of pro- and anti-saccades under gap and overlap conditions is currently investigated intensively in neurodevelopmental disorders such as ASD and ADHD (Rommelse, Van der Stigchel, & Sergeant, 2008).

A prosaccade, or reflexive saccade, is a rapid eye movement in response to a visual stimulus of abrupt onset. It serves to bring the image of an object of interest onto the fovea.

An antisaccade is a saccadic eye movement in the opposite direction to a peripheral target. It has been well studied for examining response monitoring, response preparation, and response inhibition. Response inhibition, or the suppression of prepotent, but contextually inappropriate behaviours, is essential to adaptive, flexible responding. It requires suppression of the prepotent response of looking towards a suddenly appearing visual stimulus and substitution with the novel behaviour of looking in the opposite direction. As a result, Denckla suggested that the antisaccade task has several features which make it qualified as a test of executive function (Denckla, 1996).

This simple task yields several measures such as the error rate which is reflecting inhibitory problems, i.e. a failure to suppress an inappropriate response, and therefore can provide important insight into the integrity of the cognitive and neural mechanisms involved in the volitional control of behaviour (Hutton & Ettinger, 2006).

Average antisaccade error rate in healthy humans vary considerably across studies. Recent studies using large samples suggest an error rate of around 20% is typical (Ettinger et al., 2003; Ettinger et al., 2005; Tatler & Hutton, 2007). Error rates are not constant across the lifespan; they are highest during childhood, reaching a nadir during early adulthood, and then increasing very slowly with advancing age until around 60, when the rate of increase appears to accelerate (Klein & Foerster, 2001; Mostofsky, Lasker, Singer, Denckla, & Zee, 2001). The developmental profile of antisaccade errors is thus broadly consistent with the known development of the prefrontal cortex.

It has been shown in previous studies that antisaccade performance is influenced by the task design. For example, antisaccade errors are typically more common, and correct antisaccade latencies are reduced, in gap trials compared to step trials, and in step trials compared to overlap trials (Fischer & Weber, 1997).

Healthy participants typically correct most of their errors (Hutton & Ettinger, 2006); however, certain pathological groups, such as those with ADHD, fail to correct a significant proportion of their errors, suggesting a deficit not only in inhibition but also error monitoring or response

generation (Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001; Munoz, Armstrong, Hampton, & Moore, 2003)(Klein, Raschke, & Brandenbusch, 2003) (O'Driscoll, et al., 2005). Antisaccade errors typically have a mean latency that is slightly shorter than those reported for prosaccades, whereas correct antisaccades typically take around 100–150ms longer to initiate than reflexive prosaccades (Munoz & Everling, 2004). This increase in the correct antisaccade latency is generally considered to reflect the additional processing required to inhibit the reflexive prosaccade and perform the necessary spatial transformations required to provide antisaccade coordinates (Olk & Kingstone, 2003).

5.4.3 Main Sequence in Saccade

In primates, it is well known that there is a consistent relationship between the duration, peak velocity and amplitude of saccadic eye movements. The peak velocity and the duration increase systematically with the amplitude of the movement. These relationships have been called the 'main sequence' (Bahill, Clark, & Stark, 1975).

Harris and Wolpert suggested that the main sequence has evolved as a strategy to optimize the trade-off between accuracy and speed. They used a semi-analytical approach and showed that there is an optimal trajectory for a given amplitude and duration; and that there is an optimal duration for a given amplitude (Harris & Wolpert, 2006).

5.4.4 Neural Substrates of Saccade Eye Movements

A number of characteristics make the saccadic system extremely useful for investigating models of cognitive control. First, the system is particularly well understood based on an extensive literature that ranges from single-unit recordings in primates (Johnston & Everling, 2008) to lesion studies in humans (Pierrot-Deseilligny, Milea, & Muri, 2004). Second, there is good convergence between that literature and human functional neuroimaging studies. Third, saccades can be measured precisely and with a number of reliable and objective parameters.

An extensive body of literature describing lesion studies, human behavioural testing, functional neuroimaging, animal neurophysiology and detailed anatomy has identified several brain areas that are involved in controlling saccadic eye movements.

5.4.4.1 Neural Substrates of Prosaccade Eye Movements

The cortical network involved in saccades is composed of areas directly triggering saccades and areas concerned with cognitive aspects of saccade control. Areas most strongly involved in triggering reflexive saccades are: (i) the parietal eye field (PEF), located in the intraparietal sulcus, (ii) the frontal eye field (FEF), located in the precentral gyrus, and (iii) the supplementary eye field (SEF) on the upper part of the medial wall of the frontal lobe (Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1998; Pierrot-Deseilligny, Rivaud, Gaymard, Muri, & Vermersch, 1995). Areas involved in cognitive aspects of saccade control are: (i) the dorsolateral

prefrontal cortex (DLPFC, has a role in inhibition of reflexive saccades) and (ii) the anterior cingulate gyrus (motivational modulation of voluntary saccades) (Gaymard, Ploner, et al., 1998; Petit et al., 1996).

Visual information enters through the retina, sent via the optic tract to the lateral geniculate nucleus (LGN) of the thalamus and then via the optic radiation to primary visual cortex. From primary visual cortex, information is sent to extrastriate cortical regions V2/V3 (in middle occipital gyrus). These brain regions are involved in mapping relevant stimuli in visual space (Dyckman, Camchong, Clementz, & McDowell, 2007; Merriam, Genovese, & Colby, 2007). From visual regions, position data (and other information relevant to subsequent motor output) travels via the dorsal stream to multiple parietal cortex regions, most prominently the superior parietal lobe and PEF (Greenlee, 2000).These parietal cortex regions have (i) direct connections to the superior colliculus (SC) (Lynch, Graybiel, & Lobeck, 1985; Pare & Wurtz, 2001), and (ii) reciprocal connections with frontal motor regions (e.g., FEF and SEF) (Barbas & Mesulam, 1981; Ferraina, Pare, & Wurtz, 2002).

Neural projections important for the generation of reflexive saccades are those from PEF to FEF and from both PEF and FEF to the SC; the SC, as well as the FEF, projects to the brainstem reticular formation.

There is considerable evidence that parietal cortex is critically important for various aspects of saccadic control. Direct projections from parietal cortex to SC suggest a role in saccade triggering. This conclusion is supported by data showing that damage to parietal cortex increases pro-saccade latencies (Gaymard, Lynch, Ploner, Condy, & Rivaud-Pechoux, 2003; Heide & Kompf, 1998).Frontal cortex is also important for motor control, eye movements included, with the FEF and SEF having direct access to the brainstem saccade-generating circuitry (Huerta, Krubitzer, & Kaas, 1986; Segraves, 1992; Yan, Cui, & Lynch, 2001). Patients with FEF lesions have increased latency of voluntary saccades, but not consistently of simple reflexive saccades (Pierrot-Deseilligny, 1991).

The cerebellar vermis, in concert with other areas, plays a crucial role in determining saccadic accuracy (Barash et al., 1999; Botzel, Rottach, & Buttner, 1993; Ettinger et al., 2002; Hashimoto & Ohtsuka, 1995; Vahedi, et al., 1995). The relative volume of the vermis was related to saccadic accuracy in humans (Ettinger et al., 2005; Ettinger et al., 2002).

The superior colliculus is involved in the generation of reflexive saccades and has been the subject of many monkey neurophysiology studies (McPeek & Keller, 2004). Supporting these studies, Neggers and colleagues (2005) found in an fMRI studies of healthy humans that collicular activity was negatively correlated with saccade latency such that greater activity in superior colliculus was associated with faster saccades (Neggers, Raemaekers, Lampmann, Postma, & Ramsey, 2005).

5.4.4.2 Neural Substrates of Antisaccade Eye Movements

It is thought that antisaccades share with simple reflexive saccades the basic saccadic circuitry, including FEF, PEF, SC, brainstem reticular formation and cerebellum. In addition, further cortical areas are likely to be required for the successful suppression of reflexive errors.

Latencies for correct anti-saccade responses are usually about 50 ms longer (Evdokimidis, Constantinidis, Liakopoulos, & Papageorgiou, 1996) than reflexive saccades, which may represent the additional computations necessary for inhibition and/or the co-ordinate transformation process. Based on the extant literature, these additional processing requirements are supported by (i) changed activity levels in the basic saccade circuitry, and/or (ii) activity in newly recruited neural regions (Everling & Fischer, 1998; Hutton & Ettinger, 2006; Munoz & Everling, 2004).

A number of studies have focused on a group of patients with acquired brain lesions in order to identify the roles of specific cortical regions in antisaccade performance. The most consistent findings from this literature are (a) increased antisaccade latencies following FEF lesions and (b) increased error rates following DLPFC lesions (Pierrot-Deseilligny, Ploner, Muri, Gaymard, & Rivaud-Pechoux, 2002). However, there is also evidence of increased error rates after damage to ventral prefrontal cortex (Walker, Husain, Hodgson, Harrison, & Kennard, 1998), superior colliculus, and anterior cingulate (Gaymard et al., 1998).

Functional neuroimaging studies of healthy humans have replicated these findings. Activation during antisaccades has been observed most consistently in DLPFC (Ettinger et al., 2008; Muri et al., 1998; Sweeney et al., 1996) and FEF (Cornelissen et al., 2002).

Ettinger et al. (2008) studied 17 healthy volunteers on prosaccade and antisaccade tasks. They found that the right supramarginal gyrus showed significantly greater activation during the inhibition phase than the generation phase for both antisaccade and prosaccade trials, suggesting a role in saccade inhibition or stimulus detection. Moreover, they reported the involvement of right lateral FEF and bilateral intraparietal sulcus in antisaccade generation. In their study, the ventrolateral and dorsolateral prefrontal cortices showed comparable levels of activation in both phases of the task, suggesting a more general supervisory role of these areas in the volitional control of eye movements, such as stimulus appraisal, task set, and decision making (Ettinger, et al., 2008).

Cornelissen et al. (2002) showed that there was an increase in the FEF activity before initiation of correct antisaccades but not error saccades, likely indicating presaccadic inhibitory processes (Cornelissen, et al., 2002).

5.4.5 Studies on Prosaccade and Antisaccade Tasks in ASD

Given that the major impairments of autistic children lie in social ability and communication, the majority of eye movement studies in ASD have focused on scan patterns of social scenes and facial expressions. However, there are some studies which have investigated saccadic eye movements as measured by the prosaccade and antisaccade tasks, aiming to assess basic oculomotor behaviour in children with ASD.

5.4.5.1 Prosaccade Eye Movements in ASD

Findings in attentional patterns using the gap/overlap paradigm, prosaccade task in ASD are contradictory (Rommelse, Van der Stigchel, & Sergeant, 2008). It is not clear whether children with ASD have difficulties with attentional engagement. Two studies investigating this had conflicting results: one study found a significant difference in gap effect between the two groups (van der Geest, et al., 2001) and the other study did not (Goldberg et al., 2002).

In a study by van der Geest, the eye movements of a group of children with HFA (mean age of 10.9 years) were recorded using electrooculography (EOG). Their task consisted of 120 trials (60 Gap and 60 Overlap trials) presented in 2 blocks. They found that autistic children showed a reduced gap effect compared to the control children. They explained this reduced gap effect by suggesting a lower level of engagement in the attentional system of autistic children; however, shorter overall SRTs were not observed in the autistic children. Furthermore, as the overall SRT did not become slower, they also concluded that there were no specific problems in attentional disengagement (van der Geest, et al., 2001).

In a study by Goldberg (2002), eye movements were recorded in a group of children with HFA (mean age of 13.8 years) and controls on a Gap/Null/Overlap Paradigm which consisted of 75 trials (25 trial for each condition). They reported a slower SRT in the HFA group compared to controls, but they did not find a significant gap effect in HFA (Goldberg, et al., 2002).

A third study by Landry and Bryson (2004) found latency differences in a group of young children with autism (mean age=5.6 years) on overlap trials, but not on gap trials (Landry & Bryson, 2004), suggesting difficulties disengaging attention from the fixation point in the autism group. However, it should be noted that the study design by Goldberg and Landry was different from the current study as in their study there was no explicit task instruction to look at the peripheral stimulus.

Similar studies have also been carried out in adults with ASD. For example, Kawakubo in a group of male and female adults with autism (mean age=29 years), showed that the ASD group had significantly fewer correct trials in both gap and overlap conditions. In the overlap condition, the express saccade occurred more frequently in the ASD group while in the gap condition, the mean express saccade rate showed no difference between two groups. In the

control group, as expected, the express saccade was rarely observed in the overlap condition, and frequently observed in the gap condition. They concluded that individuals with ASD have deficiencies in attentional engagement (Kawakubo, Maekawa, Itoh, Hashimoto, & Iwanami, 2004).

Saccade velocity has not received much attention in previous literature on prosaccade eye movement in ASD. Rosenhall et al. (1988) investigated visually-guided saccades in children with autism (N=11, age: 9–16 years, having normal to below normal intelligence) and found that six of the children with autism had hypometric (i.e. small) saccades, with four of these six having reduced saccade velocities compared with control group (Rosenhall, Johansson, & Gillberg, 1988). However, it is important to note that their control group had a normal intelligence.

In contrast to Rosenhall et al. (1988) , Minshew et al. (1999) found that saccade latency, accuracy, duration, and peak velocity were normal in individuals with autism (N=26 with FSIQ>80) in a visually guided saccade task (Minshew, Luna, & Sweeney, 1999). Similarly, Goldberg et al. (2002) did not find any group differences in saccade amplitude or peak velocity (Goldberg, et al., 2002).

5.4.5.2 Antisaccade Eye Movements in ASD

A second important task in the context of saccadic impairment in childhood disorders is the antisaccade task. Individuals with ASD consistently show deficient response inhibition while performing antisaccades.

The results were inconsistent as to whether children with ASD are slower to execute a correct antisaccade: one study failed to find an effect (Goldberg, et al., 2002); whereas the other study found that a younger group of individuals with ASD were even faster to initiate a correct antisaccade than controls (Luna, Doll, Hegedus, Minshew, & Sweeney, 2007).

Individuals with ASD, have consistently shown an increased rate of antisaccade errors (i.e. a failure to suppress the prepotent prosaccade) (Goldberg, et al., 2002; Luna, et al., 2007; Minshew, et al., 1999). In a study by Luna et al. (2007), developmental changes in saccadic eye movements in a group of individuals with ASD (age range: 8-33 years, mean IQ=110.74±16.84) were explored. They found that the basic deficit in response inhibition such as a higher number of antisaccade direction errors, were present throughout development in the ASD group (Luna, et al., 2007).

Thakkar, in an fMRI study, investigated response monitoring in a group of adults with ASD using an antisaccade task. Deficiencies in this function and abnormalities in the ACC have been reported as contributing factors to autistic disorders. They found that relative to controls, ASD participants: (i) made more antisaccade errors and responded more quickly in correct trials; (ii) showed reduced discrimination between error and correct responses in rostral ACC. Their

findings demonstrated functional and structural abnormalities of the ACC in ASD that may compromise response monitoring and thereby contribute to behaviour that is rigid and repetitive rather than flexible and responsive to contingencies (Thakkar, et al., 2008).

Previous studies have found no differences in antisaccade velocity in ASD compared to controls (Goldberg, et al., 2002; Minshew, et al., 1999).

5.4.6 Studies on Prosaccade and Antisaccade Tasks in ADHD

The hypothesis that children with ADHD have problems with response inhibition is partly revealed through research using antisaccade tasks which is a suitable measure to investigate whether reflexive motor inhibition is indeed affected in ADHD.

5.4.6.1 Prosaccade Eye Movements in ADHD

The reports on prosaccade latencies are consistently more variable in ADHD compared to controls (Klein, et al., 2003; Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001; Munoz, Armstrong, Hampton, & Moore, 2003; O'Driscoll, et al., 2005). The study with the largest sample of ADHD patients (N=76, from 6-59 years of age) found longer and more variable latencies, reduced peak velocity and increased saccade durations compared to controls (Munoz, et al., 2003). However, this finding was not confirmed in studies with smaller sample sizes (Hanisch, Radach, Holtkamp, Herpertz-Dahlmann, & Konrad, 2006; Karatekin & Asarnow, 1998; Mostofsky, Lasker, Cutting, et al., 2001; O'Driscoll, et al., 2005). In a study by Munoz et al., SRT for both ADHD and control groups was significantly increased in the overlap condition compared with the gap condition and they did not find any difference in gap effect between ADHD and control groups (Munoz, et al., 2003).

Taken together, prosaccade latency is more variable and possibly slower in children with ADHD, presumably indicating that children with ADHD have difficulty in regulating processes of saccade initiation.

5.4.6.2 Antisaccade Eye Movements in ADHD

The results of antisaccade performance in ADHD are somewhat inconsistent, although the studies that found an elevated number of antisaccade errors are in the majority (Mostofsky, Lasker, Cutting, et al., 2001) (Munoz, et al., 2003; O'Driscoll, et al., 2005) (Klein, et al., 2003), indicating that children with ADHD are less able than controls to suppress inappropriate oculomotor responses.

A few studies, however, did not support this finding (Aman, Roberts, & Pennington, 1998; Hanisch, et al., 2006). Low statistical power and differences in the tasks might be to blame for the lack of effect observed in antisaccade errors in these studies. For example, in the study by Aman et al., a different version of the antisaccade task was used. Although this could account

for the lack of effect, it must be noted that patients still committed 10% more direction errors than controls in that study (Aman, et al., 1998).

In the study by Munoz, in an antisaccade task, ADHD participants (age 6-16 years) had greater difficulty suppressing reflexive prosaccades toward the eccentric target, and had increased reaction times for correct antisaccades, and greater intra-subject variance (Munoz, et al., 2003). Klein showed that during the antisaccade tasks, ADHD patients (age 7-15 years, both males and females) exhibited generally larger proportions of direction errors than controls. Overall, patients corrected fewer of the direction errors than controls, and SRT's were generally slower in patients than in controls (Klein, et al., 2003).

Increased variability of antisaccade reaction time has been reported in ADHD compared with control groups in previous studies(Karatekin, 2006; Karatekin, Bingham, & White, 2010) Karatekin et al. (2010) compared 26 individuals with ADHD (mean age=145months, mean FSIQ=106 with the male to female ratio of 77:32) with a group of age and IQ-matched controls (N=48) and a group of participants with youth-onset psychosis (N=29, mean age=178 months). They reported that the psychosis group, but not the ADHD group had elevated antisaccade error rates; however, variability of error rates was high in both groups. These inhibitory failures were accompanied by a lower level of momentary cognitive effort (as indexed by pupillary dilations). Interestingly, the largest differences between the control and clinical groups were found not in the expected indices of inhibition but in the probability of correcting inhibitory errors and in the variability of antisaccade reaction time. The authors suggested that the failure to correct antisaccade and increased RT variability were related to attentional fluctuations in both clinical groups (Karatekin, et al., 2010).

5.4.7 Factors Affecting Antisaccade Performance in ADHD

There are a number of variables that influence antisaccade performance in individuals with ADHD, including developmental effects, ADHD subtype, and medication (Rommelse, Van der Stigchel, & Sergeant, 2008). Klein showed that children with ADHD did not show the normal age-related decrease in latency for correct antisaccade responses, suggesting an abnormal pattern of development of antisaccade performance in affected children (Klein, et al., 2003).

ADHD subtype is another factor that seems to affect performance. O'Driscoll et al compared the ADHD-combined subtype with the ADHD-inattentive subtype on antisaccade performance and showed that participants with the combined subtype were significantly more impaired than those with the inattentive subtype, who did not show any impairment. They concluded that the deficits in inhibiting eye movements might be mediated by brain structures implicated specifically in the hyperactive/impulsive symptoms of ADHD (O'Driscoll, et al., 2005).

Based on the fact that one of the possible effects of methylphenidate is an increase in inhibitory control through its effect on fronto-subcortical pathways (Faraone & Biederman, 1998), some researchers investigated whether performance on the antisaccade task improves with administration of the stimulants.

Klein et al. tested the effect of methylphenidate using a repeated measurement design. 27 boys with ADHD (mean age 12.6 years) were randomly assigned to two testing order conditions (first on-, second off-medication versus first off-, second on-medication) and performed the prosaccade and the antisaccade tasks (200 trials each). Methylphenidate showed beneficial effects by reducing pro- and antisaccadic reaction times, error correction times, and the proportion of direction errors during the antisaccade task (Klein, Jr Fischer, Fischer, & Hartnegg, 2002). Their finding was then confirmed by O'Driscoll for both combined and inattentive subtypes of ADHD (O'Driscoll, et al., 2005).

5.5 Summary

There are only a few studies that have compared EF in children with diagnosis of ASD and ADHD in an attempt to identify cognitive deficits specific to each disorder. Their findings are not consistent. One reason for the diverse results might be the differences in the age ranges each study adopted or the different types of tasks employed. Furthermore, to date, studies assessing EF deficits in both ASD and ADHD patients have not devoted a great deal of attention to the individuals having a dual diagnosis of ADHD and ASD, although as mentioned previously, the co-occurrence of the symptoms of the two disorders has been well established (Chapter 2). Consequently, there is limited information on the effect of comorbid ADHD and ASD on neuropsychological task measures. For example it is not clear to what extent the EF deficits observed in ASD groups are due to overlooked ADHD symptoms.

In addition, there is no study comparing ADHD and ASD groups on a gap/overlap paradigm using the eye tracker, a useful instrument to provide a rich data set for understanding the underlying neuropsychological mechanisms better.

5.6 Aims

This part of the study aims to replicate and extend previous findings from studies on childhood neurodevelopmental disorders. It will help to determine first whether executive dysfunction exists in the selected tasks of response inhibition (Go/No-Go and antisaccade task) in children with ADHD and ASD, and second whether the two disorders can be distinguished on the basis of performance in response inhibition.

By comparing the cognitive profile of the comorbid group with pure clinical groups, the impact of comorbidity on the EF profile can be assessed and the actual deficits caused by each one of the disorders per se can be explored. In addition, the effect of brain development on task

performance and the impact of EF deficits on the differences in the form and severity of the behavioural manifestation will be assessed.

5.7 Executive Function Measures

Two tasks of response inhibition, namely the Go/No-Go and antisaccade tasks were chosen for the purpose of this PhD study which will be presented in two separate sections, Experiment 1 and Experiment 2, in order to maximise the clarity of the presentation. At the end of the chapter, a summary of the key findings of each task with a conclusion will be presented.

5.7.1 Experiment 1: Go/No-Go Task

The task was taken from the Maudsley Attention and Response Suppression (MARS) Task battery (Rubia, Smith, & Taylor, 2007). It is a selective motor response inhibition task where a motor response has to be either executed or not.

5.7.1.1 Method

The Go/No-Go task is divided in two subtests, blocked for a right- and a left-handed response. Each block lasts for 2min 32sec. In order to familiarise participants with the task requirements, after explaining the instruction 10 practice trials were administered with performance being monitored by the experimenter: participants were provided with verbal feedback during and after the practice trials.

5.7.1.2 Procedure

For all the participants, first the right-handed block, and then the left-handed block were performed. (a) Right-handed response: Participants were asked to put their right index finger on the right arrow key and be prepared. The stimuli appeared in the middle of the screen on a black background for a duration of 300msec each, followed by a blank screen of 1300msec. The stimulus was either a green plane pointing right or a green enemy planet; participants were asked to make a response by pressing the arrow key as soon as they saw the plane, and to inhibit their motor response when the green enemy planet appeared. There were 95 trials in total: 70 Go trials (73.7% of trials) and 25 No-Go trials (26.3% of trials). (b) Left-handed response: was identical, except that all green planes pointed to the left side and participants were asked to put their left index finger on the left arrow key and a left-handed response was required.

The stimuli presentation in the Go/No-Go task was fast in order to avoid task unrelated performance decline caused by problems with delay aversion or boredom especially in the ADHD group.

The performance variables extracted from the task were mean reaction time (MRT), reaction time variability (RTSD), the percentage of premature responses, the percentage of commission errors, and the percentage of omission errors.

RT variability has been suggested to be related to fluctuations in attention or maintaining a readiness to respond (van der Meere, et al., 1996); it can therefore be a good index for sustaining attention.

Premature responses were defined as responses made in the time window between 200ms before and 100ms after stimulus onset. The criteria for premature responses were set according to Rubia's study on the MARS test battery (Rubia, Smith, & Taylor, 2007). Responses that fall into this time window are made before the type of stimulus that appeared on the screen could be seen (200ms before stimulus appearance) or registered (100ms after stimulus onset is too short to be considered an average normal reaction time). As Rubia et al. suggested it is important to analyze premature responses separately, as they could confound inhibitory and executive measures. For example, a premature response before the stimulus appears on the screen would prevent the participant from either successfully executing a response to a Go signal or inhibiting a response to a No-Go signal (Rubia, Smith, & Taylor, 2007).

Omission errors were defined as the percentage of Go trials where participants failed to respond over the total number of Go trials.

$$\textit{Omission errors} = N_{\textit{Missed Go}} / N_{\textit{Total Go}} * 100$$

The probability of inhibition was defined as the percentage of the successful inhibition in the No-Go trials over the total number of No-Go errors.

$$\textit{Probability of Inhibition} = N_{\textit{Successful No-Go}} / N_{\textit{Total No-Go}} * 100$$

Consequently, the percentage of commission error was calculated as:

$$\textit{100- Probability of inhibition}$$

5.7.1.3 Hypotheses

Based on previous neuropsychological studies, it was hypothesised that response inhibition impairment would be more pronounced in children with ADHD compared to controls and the ASD group as a higher number of commission and omission errors was expected in the former group than in the latter groups. It was also expected that individuals with ADHD would make significantly more premature responses compared to the control and ASD. It was also hypothesised that the severity of the clinical symptoms of inattention and hyperactivity/impulsivity would affect task performance.

On the basis of the study done by Sinzig (Sinzig, et al., 2008), i.e. the only study of a comorbid group in the Go/No-Go task, a similar pattern of responses inhibition was expected in the comorbid group as to the ADHD group.

5.7.1.4 Results from Go/No-Go Task

Data were available from 114 individuals including 18 ASD, 35 ADHD, 41 comorbid, and 20 controls.

One 7-year-old boy in the control group (FSIQ=133, PIQ=141, VIQ=118) was deemed an outlier in his Go/No-Go task performance (omission error points exceeding 3 *SD* above the group mean). Analyses were conducted with and without this individual. As the results changed, he was removed from further analysis. So results on Go/No-Go task are reported for 113 participants. Table 5-1 presents demographic information by group for participants who completed the Go/No-Go Task.

No significant differences in age among the groups ($p>.05$) were observed. However, significant differences were found for FSIQ, PIQ, and VIQ (all $p<.05$). Further analysis showed that the two groups of children with ADHD symptomatology (pure ADHD and comorbid groups) had significantly lower FSIQ, PIQ, and VIQ compared to controls (LSD post-hoc tests, $p<.05$), whereas the ASD group did not differ from controls (all $p>.05$). Also, the ASD group had a significantly higher FSIQ relative to the ADHD group ($p<.05$). However, no differences amongst the clinical groups were observed for PIQ and VIQ (all $p>.05$).

Table 5-1: Group descriptive for participants who completed the Go/No-Go Task: Means (SD), [Range]

	ASD (N=18)	**ADHD (N=35)**	**Comorbid (N=41)**	**Controls (N=19)**	**$F_{(3,109)}$**	**P**	**Post-hoc LSD**
Age in month	132.33(19.67)	132.26(31.89)	127.35(25.78)	126.89(29.26)	.32	.81	
[Range]	[96-168]	[84-191]	[87-200]	[92-180]			
FSIQ	111.50(16.44)	100.69(14.16)	105.59(13.30)	121.00(13.76)	9.17	<.001	Controls> ADHD, Comorbid*
[Range]	[77-139]	[70-135]	[79-142]	[102-149]			ASD>ADHD*
PIQ	108.17(14.96)	99.00(13.85)	104.02(13.33)	113.89(11.56)	5.45	.002	Controls> ADHD, Comorbid*
[Range]	[80-136]	[64-131]	[75-141]	[100-136]			
VIQ	112.44(19.00)	102.34(15.89)	105.83(14.75)	123.26(15.02)	7.97	<.001	Controls> ADHD, Comorbid*
[Range]	[78-145]	[75-133]	[77-146]	[99-151]			

**Post-hoc test, p<.05*

5.7.1.4.1 Group Comparisons on the Go/No-Go Task

Initially, analyses were conducted without adjusting for age and IQ. Group differences were explored using ANOVA with 'group' as the between-subjects factor. Due to positive skewness, premature responses and omission errors data were transformed using square root transformation.

Group descriptive for these individuals are presented in Table 5-2 and Table 5-3 showing the effect sizes for pairwise comparisons.

No significant group differences were found in the mean reaction time ($F_{(3,109)}$=.32, p=.80, η^2=0.009) and RT Variability ($F_{(3,109)}$=1.57, p=.20, η^2=0.041). For RT variability, a medium effect size of the difference was observed between ADHD and controls (d=.53), between the comorbid and control group (d=.32), and also between ADHD and ASD groups (d=.42); however, the power of these analyses was limited for a .05 two-sided level of significance (power=.47, power=.21, and power=.27, respectively).

A significant effect of group was detected in the percentage of premature responses ($F_{(3,109)}$=4.07, p=.009, η^2=0.101). Post-hoc analysis showed a significantly higher number of premature responses in ADHD and comorbid groups compared to controls (LSD Post hoc: p=.004 for ADHD and control comparison and p=.002 for comorbid and control comparison). There were no significant differences between the ASD and control group on premature response (p>.05). Also, the ASD group did not show significant differences from ADHD and comorbid groups on this variable (p>.05), even though the effect sizes of the differences were medium (Table 5-3). The power of these analyses was limited for a .05 two-sided level of significance (power=.34 for ADHD and ASD comparison, and power=.39 for comorbid and ASD comparison).

On commission errors, group differences showed a non-significant trend ($F_{(3,109)}$=2.28, p=.08, η^2=0.059) with the post-hoc analysis showing a significantly higher number of premature responses in ADHD and comorbid groups compared to controls (LSD Post hoc: p=.04 for ADHD and control comparison and p=.02 for comorbid and control comparison). Large effect sizes of the difference were observed between ADHD and controls (d=.62) and also between comorbid group and controls (d=.65). It is important to mention that the power of these analyses was limited for a .05 two-sided level of significance (power=.59 for ADHD and control comparison, and power=.67 for comorbid and control comparison).

Finally, omission errors did not show any significant group differences ($F_{(3,109)}$=1.27, p=.29, η^2=0.034). Even though the effect size of the difference between ADHD and controls was medium (d=.45) for omission errors, the difference did not reach significance. However, the power of this analysis was limited for a .05 two-sided level of significance (power=.40).

As the two groups with ADHD showed the same pattern of performance, they were then combined in one group and the analysis was repeated comparing the 3 groups: ASD group (N=18), the group with ADHD (N=76), and controls (N=19). In this reanalysis, again no significant group differences were detected in MRT, RT variability, and omission errors (p>.05); however, there was a trend towards a significantly higher RT variability in the combined group with ADHD compared to controls (p=.09, d=.43) The pattern of difference in premature responses ($F_{(2,110)}$=6.13, p=.003, η^2=0.100) was as before and the combined ADHD group showed a significantly higher number of premature responses compared to controls (LSD Post hoc: p=.003). However, this time, commission errors showed a significant difference between groups ($F_{(2,110)}$=3.39, p=.04, η^2=0.058). As the sample sizes were very different, Hochberg's GT2 was used which showed a significantly higher rate of commission errors in the combined group with ADHD than controls (p=.04).

Although the groups did not differ in age, it might still be assumed that neuropsychological performances improve with age due to brain maturation (Happe, et al., 2006; Luna, et al., 2007). IQ is also associated with neuropsychological performance (Ozonoff et al., 2004). Therefore, the effect of age and IQ was evaluated using an ANCOVA on Go/No-Go variables with group as the between-subjects variable and age and FSIQ as covariates.

When adjusted for age, the findings did not substantially differ from the unadjusted analyses and when adjusted for FSIQ, the findings were slightly attenuated but again were not different from unadjusted analyses. Finally, all the analyses were repeated with both age and FSIQ entered as covariates. Again, no differences from the unadjusted analyses were observed (as the findings did not change after controlling for age and FSIQ, in order not to be repetitive, the statistics were not reported).

Table 5-2: Group comparisons on Go/No-Go Task measure: Means (SD)

	ASD (N=18)	ADHD (N=35)	Comorbid (N=41)	Control (N=19)	Group effect		Post-hoc LSD
					$F_{(3,109)}$	P	
Mean Reaction Time (msec)	358.16(68.15)	356.38(71.52)	343.72(56.09)	353.42(71.04)	.32	.80	
RT Variability	131.63(44.07)	155.87(69.31)	140.02(57.57)	120.47(63.37)	1.57	.20	
Premature Responses (%)	4.18(4.89)	6.44(5.29)	6.80(6.72)	2.85(4.72)	4.07	.009	ADHD, Comorbid>Controls*
Commission Errors (%)	45.78(17.57)	51.18(16.50)	52.59(19.37)	40.74(16.95)	2.28	.08	
Omission Errors (%)	4.80(4.92)	6.39(6.70)	5.23(5.19)	3.83(4.29)	1.27	.29	

** Post-hoc test, p<.05*

Table 5-3: Effect sizes (d) of Go/No-Go Task measures

	ASD-Control	ADHD-Control	Comorbid-Control	ADHD-ASD	Comorbid-ASD	Comorbid-ADHD
Mean Reaction Time (msec)	.06	.04	-.15	-.02	-.23	-.20
RT Variability	.20	.53	.32	.42	.16	.25
Premature Responses (%)	.28	.72	.68	.44	.44	.06
Commission Errors (%)	.29	.62	.65	.32	.37	.08
Omission Errors (%)	.21	.45	.29	.27	.08	-.19

5.7.1.4.2 Effects of Age and IQ

Table 5-4 shows the correlation between the task variables, age and FSIQ across all groups. Overall, age was significantly correlated with all the task measures, while FSIQ was only significantly correlated with commission and omission errors. Table 5-5 shows the correlation between the Go/No-Go task variables, age and FSIQ for each group.

Fisher's *r*-to-z transformation did not show any differences in the magnitude of correlation between FSIQ and performance variables between the four groups (all $p>.05$).

Figure 5-1 depicts developmental changes in RT in the four groups of participants. The correlation between age and RT was significant in all groups indicating a faster RT in older individuals with no difference in the magnitude of the correlation coefficients between groups as was tested by Fisher's *r*-to-z transformation ($p>.05$).

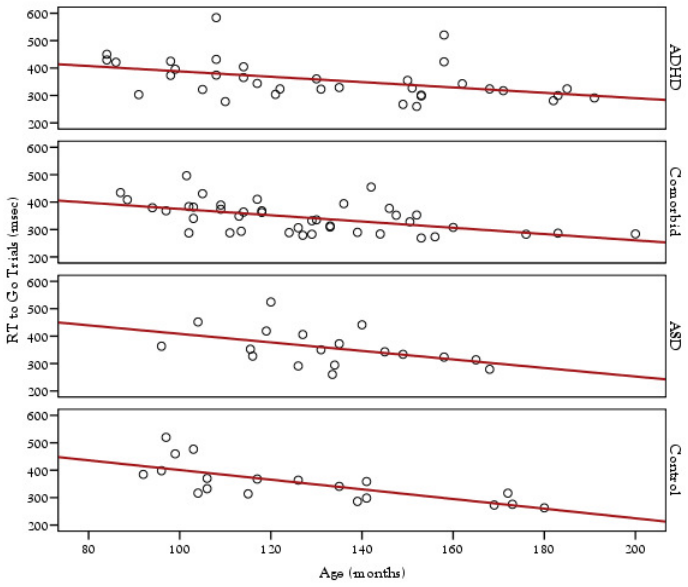


Figure 5-1: Developmental changes in Reaction Time in Go/No-Go Task

In Figure 5-2, developmental changes in premature responses in each group are shown. The correlation between age and premature responses was only significant in ADHD and the control group, showing a lower number of premature responses in the older group. No difference in the magnitude of the correlation coefficients was detected between these two groups ($p>.05$). The effect of age on premature responses was greater in the control than ASD ($z=3.03$, $p=.002$) and comorbid ($z=2.35$, $p=.02$) groups and also in the ADHD than comorbid ($z=2.38$, $p=.02$) groups but not than the ASD group ($p>.05$).

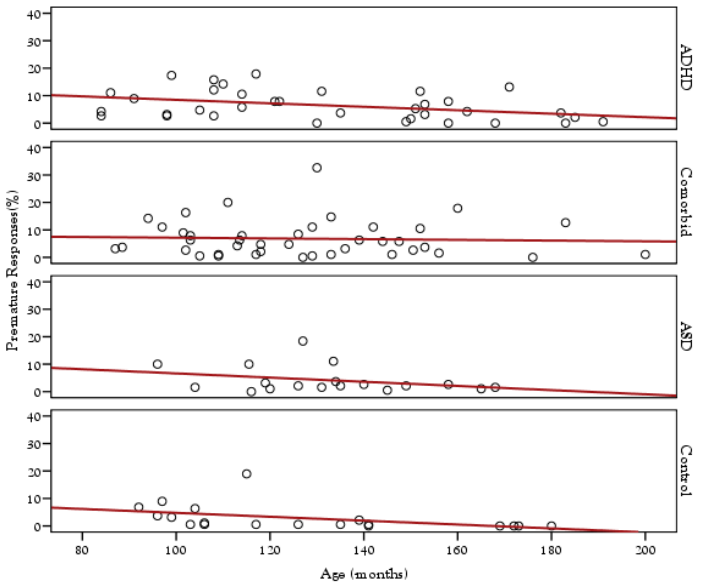


Figure 5-2: Developmental changes in Premature Responses in Go/No-Go Task

Figure 5-3 shows age improvement in the commission error rate. Only the ADHD and control groups showed a significant age effect on the rate of errors and both groups clearly showed a lower rate of commission errors in older participants. No difference in the magnitude of the correlation between the four groups was detected (p>.05).

Finally, in Figure 5-4 the developmental improvement in omission errors is depicted by group. A significant correlation was detected in control and comorbid groups; however Fisher's r-to-z transformation did not show any differences in the magnitude of correlation between the four groups (p>.05).

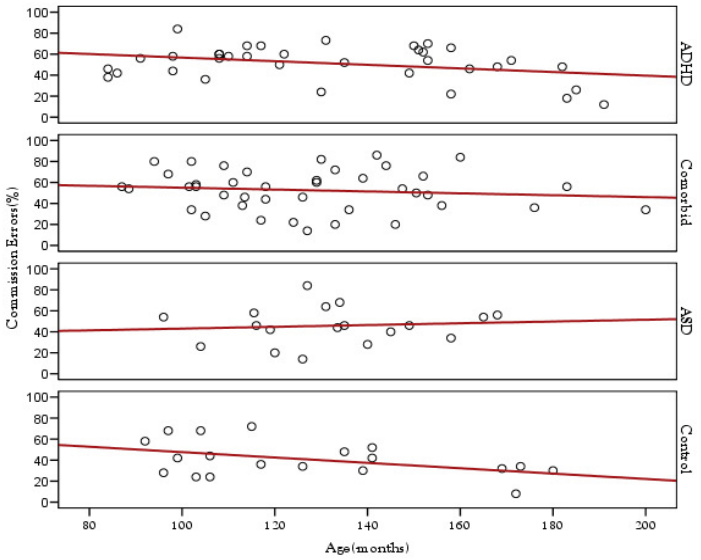


Figure 5-3: Developmental changes in Commission Errors in Go/No-Go Task

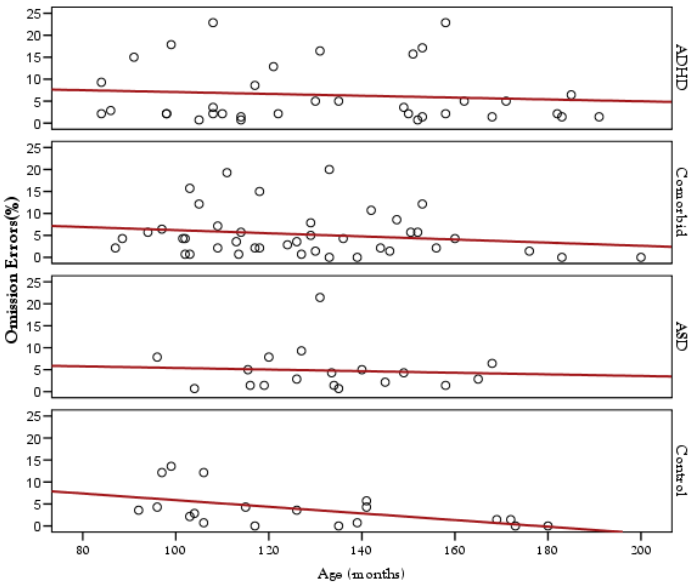


Figure 5-4: Developmental changes in Omission Errors in Go/No-Go Task

Table 5-4: Correlation between Go/No-Go Task measures, age and IQ across all Groups

	MRT (msec)	RT Variability	Premature Responses (%)	Commission Errors (%)	Omission Errors (%)
Age	-.50**	-.44**	-.31**	-.21*	-.22**
FSIQ	.02	-.07	-.13	-.16*	-.21*

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level*

Table 5-5: Correlation between Go/No-Go Task measures, age and FSIQ for each group

	Age*RT	FSIQ*RT	Age*Premature Reponses	FSIQ* Premature Reponses	Age* Commission Errors	FSIQ* Commission Errors	Age* Omission Errors	FSIQ*Omission Errors
ASD	-.45*	-.19	-.27	-.37	.09	.05	-.04	-.14
ADHD	-.45**	.02	-.43**	-.003	-.33*	-.14	-.10	-.18
Comorbid	-.53**	-.14	-.11	.23	-.12	-.02	-.28*	-.23
Control	-.73**	.51*	-.67**	-.10	-.44*	-.21	-.57**	.08

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level*

5.7.1.4.3 Effect of Handedness on Task Performance

The Go/No-Go task involves motor responses and since our study was run for right and left hand, separately, data on handedness were also collected. Overall, from 114 individuals (including 3 patient groups and controls), 95 individuals (83.3%) were right handed and 19 (16.7%) were left handed. No effects of handedness were detected on the task performance (Fisher's exact test=4.98, p=.16).

5.7.1.4.4 Correlation between Task Measures

Table 5-6 shows the correlation between the Go/No-Go task variables across all groups. RT variability was significantly correlated with premature responses (r=.62, p<.001), commission errors (r=.50, p<.001), and omission errors (r=.52, p<.001). Omission errors were significantly correlated with commission errors (r=.38, p<.001) and premature responses (r=.37, p<.001). Moreover, the correlation between commission errors and premature responses (r=.70, p<.001) was significant.

The pattern of correlation when conducted further within each group was the same as in the whole group.

Table 5-6: Correlation between Go/No-Go Task measures

	RT Variability	**Premature Responses (%)**	**Commission Errors (%)**	**Omission Errors (%)**
Mean Reaction Time (msec)	.63**	.05	-.009	.25**
RT Variability		.62**	.50**	.52**
Premature Responses (%)			.70**	.37**
Commission Errors (%)				.38**

***Correlation is significant at the 0.01 level*

5.7.1.4.5 Correlations between Task Measures and Clinical Measures by Group

Correlations between Go/No-Go task measures and clinical measures including Conners score, SCQ, and selective scores of SDQ (SDQ total score and SDQ hyperactivity) were assessed across the groups (see Table 5-7).

Table 5-7: Correlation between Go/No-Go task measures and clinical measures across all groups

	Conners Inattention	Conners Hyperactivity /Impulsivity	SCQ	SDQ Total	SDQ Hyperactivity
RT (msec)	.09	.01	-.11	-.11	-.02
RT Variability	.26**	.13	-.08	.07	.14
Premature Responses	.37**	.24**	.21*	.29**	.23*
Commission Errors (%)	.22*	.09	.09	.22*	.20*
Omission Errors (%)	.22*	.13	-.03	.19*	-.02

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level*

Analysis of correlation was then conducted within each group (see Table 5-8). In the control group, a significant correlation was observed for RT variability and Conners hyperactivity/impulsivity score (r_s=.52, p=.01) and between premature responses and Conners inattention score (r_s=.59, p=.004), indicating more variable and more premature responses in the individuals with higher rates of inattention and hyperactivity. Premature responses were correlated with the SDQ total score (r=.79, p=.003) and SDQ hyperactivity subscales (r=.62, p=.03). A high correlation was also detected for commission errors with SDQ total score (r=.69, p=.01) and SDQ hyperactivity subscales (r=.67, p=.02). However, when age and FSIQ were controlled for, the correlations with SDQ were no longer significant.

In the ASD group, no correlation was found between Go/No-Go task measures and symptoms of autism as measured by ADOS and ADI-R (all p>.05).

The ADHD group showed a significant correlation for RT variability and Conners inattention score (r_s=.35, p=.02), reflecting more variable responses in the individuals with a higher inattention score. Omission errors were correlated with the SDQ total score (r=.37, p=.02) and Conners hyperactivity/impulsivity score (r_s=.29, p=.04). In addition, a moderate correlation was observed for the RT with PACS inattention score (r=.42, p=.005) and PACS hyperactivity score (r=.37, p=.01) indicating that as the severity of inattention and hyperactivity symptoms increased, the response time similarly increased. Moreover, PACS hyperactivity was correlated with premature responses, (r=.34, p=.02), and omission errors (r=.37, p=.01). All of the correlations remained significant even when the effect of age and FSIQ were controlled for.

Finally, in the comorbid group, the relationship between Go/No-Go task measures and symptoms of autism as well as ADHD symptoms was assessed. There was only a significant correlation between omission errors and Conners inattention (r_s=.38, p=.007), reflecting that the individuals with more symptoms of inattention, failed to respond to higher number of Go trials.

Autism symptomatology had an affect on task performance in this group. A significant correlation was observed between premature responses and the ADOS communication score (r=.35, p=.01). Moreover, commission errors were significantly correlated with the ADOS communication score (r=.37, p=.01) and ADOS social score (r=.29, p=.03). Correlations remained significant after removing the effect of age and FSIQ.

Table 5-8: Correlation between Go/No-Go Task measures and clinical measures for each group (Unadjusted for age and FSIQ)

	RT (msec)	RT Variability	Premature Responses	Commission Errors (%)	Omission Errors (%)
Controls					
Conners Inattention	.38	.33	.59**	.10	.19
Conners Hyperactivity /Impulsivity	.49*	.52*	.38	.15	.28
SCQ	.32	.05	.10	.004	.25
SDQ Total	.08	.27	.79**	.69*	.21
SDQ Hyperactivity	.15	.23	.62*	.67*	.09
ASD					
Conners Inattention	-.12	.001	.30	.09	-.10
Conners Hyperactivity /Impulsivity	-.16	-.12	.32	-.13	.14
SCQ	-.22	-.07	.3	.11	.009
SDQ Total	-.78**	-.47	.10	.32	.49
SDQ Hyperactivity	-.45	-.17	.08	.28	-.41
ADHD					
Conners Inattention	.22	.35*	.27	.07	.08
Conners Hyperactivity /Impulsivity	.26	.20	.11	-.19	.29*
SCQ	-.20	-.27	.09	-.17	-.32*
SDQ Total	-.07	-.14	-.06	-.03	-.37*
SDQ Hyperactivity	.17	.07	-.06	.02	.02
Comorbid					
Conners Inattention	.11	.14	.10	.13	.38**
Conners Hyperactivity /Impulsivity	-.19	-.17	-.09	.05	-.08
SCQ	-.07	-.14	-.03	-.09	-.06
SDQ Total	.02	.19	.27	.30	-.16
SDQ Hyperactivity	-.13	-.13	-.05	-.01	-.15

**Correlation is significant at the 0.05 level,* ***Correlation is significant at the 0.01 level*

5.7.1.5 Discussion of the Go/No-Go Task

Executive function deficits have been reported in a wide variety of neurodevelopmental disorders, including autism and ADHD. The aims of this part of the study were: 1) to investigate the EF profile in ADHD and ASD groups on the Go/No-Go task relative to a group of healthy controls, 2) to examine whether the two disorders can be distinguished on the basis of their ability for response inhibition, 3) to assess the impact of comorbidity on task performance, and finally 4) to explore to what extent the EF deficits explain differences in the form and severity of behavioural symptoms.

With regard to the first aim, the ADHD group showed deficits of response selection/inhibition on the Go/No-Go task, whereas the ASD group did not show any differences in their performance compared to the controls. This might suggest a different EF profile in individuals with ASD and ADHD. This finding is partly in line with findings of previous studies. For example, Ozonoff and Happé found more pronounced deficits in response inhibition for ADHD children than for ASD children (Happe, et al., 2006; Ozonoff & Jensen, 1999), whereas Johnson and Geurts revealed the same level of response inhibition deficits for both groups (Geurts, et al., 2004; Johnson, Robertson, et al., 2007).

Nevertheless, inhibition deficits in children with ASD have been consistently reported in previous studies (Geurts, et al., 2004; Happe, et al., 2006; Ozonoff & Jensen, 1999). However, this finding was not replicated in the present sample. One explanation for that could be the fact that the previous studies have not evaluated their ASD group for ADHD symptomatology which can confound their findings as it is not clear to what extent the response inhibition deficits observed in their ASD group are due to overlooked ADHD symptoms.

An interesting finding in the present sample was that the pattern of deficit in the comorbid group was largely similar to the ADHD group which in turn would suggest that the inhibition impairment in ASD individuals reported in previous studies could be to some extent due to the unmeasured comorbid ADHD. This could imply that the neuropsychological correlate of ADHD in the presence of ASD is similar to ADHD on its own.

It is important to note that even though the Go/No-Go task was sensitive enough to separate individuals with ADHD from the controls; it lacked the power to differentiate the clinical groups from each other. However, the lack of findings could be explained by the limited power of the study as the sample size was relatively small and unequal and the ASD group had the smallest sample size in the present study.

As it was predicted, the poor inhibitory performance was observed in children with ADHD symptomatology (pure ADHD and comorbid group) in the Go/No-Go task. The poor inhibitory response was mostly evident with regard to commission errors and premature

responses, which are measures of impulsivity. The higher number of commission errors and premature responses demonstrates the difficulty of inhibiting the prepotent response. This finding is consistent with previous studies which showed premature responding in ADHD patients during different tasks of time estimation (Smith, Taylor, Rogers, Newman, & Rubia, 2002), sustained attention (Rosenbaum & Baker, 1984) and motor inhibition (Happe, et al., 2006; Rubia, Smith, & Taylor, 2007; Rubia, Taylor, et al., 2001).

A higher rate of omission errors, which is a measure of inattention, has been consistently reported in the ADHD groups in previous studies (Happe, et al., 2006; Rubia, Smith, & Taylor, 2007). This finding, however, was not replicated in the current study which can be partly explained by the task design. The event rate (the presentation rate of stimuli) in the Go/No-Go is quite fast, and this might bias the children to commit more errors rather than omit the appropriate responses. It has been well-documented that task manipulation with factors such as event rates (Andreou, et al., 2007; Konishi, et al., 1998) or rewards (Konrad, et al., 2000) (Andreou, et al., 2007) can substantially improve the performance of children with ADHD, in some cases to the level of controls. Given the sensitivity of individuals with ADHD to task parameters, Kuntsi suggested that children with ADHD do not show a stable deficit across varying task conditions (Kuntsi, Wood, Van Der Meere, & Asherson, 2009).

Increased intra-subject reaction time variability (RTSD) has been replicated highly consistently in ADHD literature (Klein, et al., 2006; Kuntsi, McLoughlin, et al., 2006). Several theories have been proposed to explain RT variability such as a temporal processing deficit (Castellanos & Tannock, 2002), inefficiency in the use of attention by executive control processes (Bellgrove, et al., 2005), a non-optimal arousal state that leads to inconsistent performance across different cognitive tasks (Sergeant, et al., 2003), and frequent lapses in attention (van der Meere, et al., 1996). In the current sample, increased RT variability has been observed in the two groups with ADHD compared to controls and the ASD group with medium effect sizes in the differences. However, possibly due to the limited power, the group differences did not reach significance. Increased RT variability in the two groups with ADHD may suggest attentional fluctuations.

The two groups with ADHD not only showed a tendency for more variable reaction times, but they were also making more commission errors. This pattern of responding (variable and inaccurate) was in agreement with the pattern van der Meere identified in his review as characteristic of hyperactivity. Children with ADHD seem to have frequent lapses in attention and are often inconsistent in how they perform (van der Meere, et al., 1996).

The effect of cognitive ability on the task performance was similar in all groups. Some of the tasks' measures were related to the age of the participants, albeit with different strengths. Except for the premature responses that showed a more pronounced effect of age in control and ADHD groups compared to the ASD group, no differences were observed between the

groups in developmental improvements on task performance. However, as it is demonstrated in figures 5.1–5.4, there is more variation in the clinical groups compared to the controls. So while the scores in the control group fall along the line showing age related improvement, the scores of the clinical groups are very variable and show less of a relationship with age. It is therefore recommended to consider individual variation within groups, as group means can hide heterogeneity, or the possibility of subgroups with different types of impairment.

It is important to note that cross-sectional investigations such as this study cannot definitively address the developmental maturation in executive function as longitudinal studies are needed to investigate developmental changes in more depth.

Compared to the previous studies using the same version of the Go/No-Go task (Happe, et al., 2006; Rubia, Smith, & Taylor, 2007), the number of commission errors was relatively higher in the present study. Rubia et al. (2007) reported 28% and 19% of commission errors in their ADHD and control groups, respectively (Rubia, Smith, & Taylor, 2007) and Happé et al. reported 37.8%, 49.9%, and 41.5% of commission errors in their ASD, ADHD, and control groups, respectively (Happe, et al., 2006). The relatively poor performance of the participants in the current study might be partly due to the lengthy test battery administered and the consequent fatigue that would likely affect the individual's performance.

The correlations between task measures showed that premature responses were associated with commission errors which could suggest that response prematurity and poor inhibitory control are closely interconnected deficits, perhaps caused by a common underlying cognitive or neural deficit. In addition, commission errors were correlated with omission errors albeit modestly, which is in line with the suggestion that the ability to sustain attention may be an important underlying factor for the cognitive processes involved in inhibition tasks (Muri, Rivaud, Timsit, Cornu, & Pierrot-Deseilligny, 1994). Interestingly, RT variability was associated with omission errors and commission errors. This might suggest that the errors are likely to have been due to attentional fluctuations.

The study also aimed to explore the association between the task measures and severity of the symptoms of ADHD and ASD. It was revealed that the performance on the Go/No-Go task was associated with symptoms of inattention, regardless of the diagnostic group. The participants with more inattentive symptoms had more variable responses and were less able to sustain their attention (as detected by a higher rate of omission errors) and inhibit their responses (as shown by increased premature responses and commission errors). It was also observed that the higher rate of hyperactivity/impulsivity and social and communication problems (as measured by SCQ) were related to premature responding.

In the control group, those individuals with higher traits of inattention and hyperactivity showed slower and more variable responses. In addition, they had more premature responding.

Consistent with the hypothesis, in the ADHD and comorbid groups, ADHD symptoms were associated with EF deficits as measured by the Go/No-Go task. This would suggest that the observed impairment in these two groups is partly due to their inattentiveness and hyperactivity/impulsivity. Moreover, in the comorbid group, having more symptoms of autism was associated with poorer Go/No-Go task performance which would suggest social and communication abilities have an effect on executive control.

5.7.1.6 Conclusion

The current study extends previous research by comparing two groups of participants with neurodevelopmental disorders, ADHD and ASD, to a group of age-matched controls. The study is one amongst very few studies which take into account the co-occurrence of the symptoms of ADHD and ASD when comparing the two groups.

The ADHD group showed deficits of response selection/inhibition in the Go/No-Go task, whereas the ASD group did not show any differences in their performance compared to the controls. While previous studies have reported inhibitory deficits in ASD, this could to some extent be due to the fact that those studies have not evaluated their ASD group for ADHD symptomatology. This could have confounded their finings as it is not clear to what extent the response inhibition deficits observed in their ASD groups may have been due to overlooked ADHD symptoms.

An interesting finding in the present sample is that the pattern of deficit in the comorbid group was to a large extent similar to the ADHD group which in turn would suggest that the inhibition impairment reported in previous studies could be to some extent due to the unmeasured comorbid ADHD.

5.7.1.7 Limitations and Suggestions for Future Research

The present study has a number of limitations. First, the sample size, although comparable to previous studies, was relatively small and unequal, and the participants' age range was quite wide. It is suggested that future research should assess the performance of individuals with ADHD, ASD and a comorbid group on a more extensive EF battery including planning, cognitive flexibility, and working memory. This would hopefully give the researchers the chance to map out distinct EF deficit profiles both quantitatively and qualitatively in these groups.

5.7.2 Experiment 2: Prosaccade and Antisaccade Tasks

Given the complexity of the oculographic method, the technical details are presented first in order not to interrupt the flow of the text when describing the individual tasks.

5.7.2.1 Technical Details of the Eye Movement Measures

5.7.2.1.1 Hardware and Laboratory Specifications

A video-oculographic eye-tracker (the SR Research Eyelink 1000) was used to track eye movements. The Eyelink 1000 Host PC performs real-time eye tracking at 1000 samples per second with no loss of spatial resolution, while also computing true gaze position on the display viewed by the individual. Stimuli were presented on a display PC during experiments. Highly accurate monocular data was acquired through a setup which involved a camera affixed to a desktop mount with the participant using a chin-rest to steady his head (Figure 5-5).

Figure 5-5: Eyelink 1000 (the SR Research)

Testing took place in a small, quiet room at the Institute of Psychiatry. Lights were dimmed in order to secure optimal recording conditions. Participants were seated in a comfortable, height-adjustable office chair in front of a 17" Display screen at 57 cm distance from the computer monitor. A vertically adjustable chin-rest was attached firmly to a desk in front of participants. Participants were instructed to rest their chins on the chin-rest while resting their arms on the desk, in order to minimise movement artefacts and to maximise comfort.

Then the camera was set up on the right eye of the participant and the position of the right eye was tracked.

5.7.2.1.2 Calibration Task

At the beginning of each task, a nine-point calibration was carried out. To perform a calibration, participants were asked to look at the fixation point first, and then to follow the stimulus as it moved on the screen.

Peripheral target locations in this calibration task were covering the corners; they were also presented at the positions equal to the eccentric targets used in each task, thereby covering the entire range of target movements across tasks.

5.7.2.2 Method

5.7.2.3 Task Orders and Stimulus Properties

First the prosaccade task and then the antisaccade task were presented in the same order to all participants. All stimuli were black and white, presented against a white background. In order to familiarise participants with the task requirements, 6 practice trials were carried out before each task, which were repeated if necessary. Performance was monitored by the experimenter and participants were provided with verbal feedback during and after the practice trials.

5.7.2.4 Prosaccade Task

The prosaccade task is a simple visuomotor baseline (or control) condition for antisaccade, designed to assess the ability of participants to generate reflexive, visually triggered saccades. It enables us to study the attentional system on a basic level and minimizes possible confounding effects of higher order cognitive or motivational factors (Fischer, Gezeck, & Hartnegg, 1997).

The task was based on the classic gap/overlap paradigm (Fischer, Biscaldi, & Gezeck, 1997; Fischer, Gezeck, et al., 1997; Gezeck, Fischer, & Timmer, 1997) which was modified for the purpose of this PhD.

5.7.2.4.1 Procedure

Participants were instructed to look from a central fixation point (FP) toward a peripheral visual target as soon as it appeared (see Figure 5-6). They were told to keep their head still while only moving their eyes. This task had 3 different conditions: gap, step, and overlap condition. The classic gap/overlap paradigm was modified by introducing the step condition as was done in the adaptation by Elsabbagh et al. (Elsabbagh et al., 2009). In this condition, the central fixation stimulus extinguishes and the peripheral target appears simultaneously. In the gap condition, a brief temporal gap of about 200ms is introduced between central and peripheral target presentation, in which the screen is blank, and in the overlap condition the peripheral target appears while the central fixation stimulus remains displayed so that the two stimuli overlap.

Each trial began with a centrally presented black circle, (0°) presentation, subtending around 0.5° x 0.5° as a FP. Regarding the temporal characteristics of FP, a fixed duration of 800msec was chosen. The peripheral target then appeared at a horizontal peripheral location (±15°), presented randomly either to the right or the left of the central fixation stimulus. Peripheral targets were small black and white shapes (a ball, leaf, bull's eye, snowflake or wheel) subtending 1° x 1° which remained displayed until the participant looked at them or until 800msec elapsed. After an interval of 500ms, the next trial commenced. The task consisted of 60 trials (Fischer, Biscaldi, et al., 1997; Fischer, Gezeck, et al., 1997; Gezeck, et al., 1997) and lasted for 4 minutes.

The performance variables from the prosaccade task are saccade reaction time (SRT) in msec, saccade velocity, and amplitude which were all computed for the directionally correct saccades only. *Correct prosaccade* was scored when the first saccade elicited by the individual was directionally correct, i.e. gaze was shifted to the peripheral target. *Prosaccade direction error* was counted when the first saccade elicited by the individual was directionally incorrect, i.e. it was away from the target. Such a saccade was considered as an error and the *error rate* (percentage) was calculated. If these errors were then corrected, the correction was captured as *correction rate*.

Finally the *gap effect* (i.e., difference in SRT between overlap and gap conditions), the effects of *disengagement* (i.e., the difference in SRT between the step and the overlap conditions) and *facilitation* (i.e., the difference between the step condition and the gap condition) as defined by Elsabbagh et al. (Elsabbagh, et al., 2009) were also assessed.

5.7.2.4.2 Hypotheses

Based on the existing prosaccade research, longer and more variable latencies and also reduced peak velocity were predicted in individuals with ADHD compared to controls. Moreover, it was hypothesised that the severity of the clinical symptoms, i.e. inattention and hyperactivity/impulsivity would affect task performance.

As discussed earlier, the findings in individuals with ASD on the prosaccade task are inconsistent and it is not clear whether children with ASD have difficulties with attentional engagement; therefore no a priori hypothesis was considered in this group in the present study.

There is no study that has compared the performance of ADHD and ASD groups directly. As a result, it is not clear whether one group will show a poorer performance than the other one. This study conducted exploratory analyses to address this question.

Moreover, no study has evaluated prosaccades in individuals with a diagnosis of comorbid ASD and ADHD and therefore no prediction was made. Instead, exploratory analyses were conducted to investigate whether participants in the comorbid group showed any difficulty in saccade initiation.

5.7.2.5 Antisaccade Task

The antisaccade task was used to test the ability of individuals to suppress reflexive saccades (a saccade in the direction of a cue) and instead generate voluntary saccades to the mirror position where no stimulus appeared (Munoz, et al., 2003). Successful performance on the antisaccade task requires two processes: the top-down inhibition of a reflexive saccade to the onset location, and the execution of a voluntary eye movement to the mirror location of the onset.

5.7.2.5.1 Procedure

The temporal and spatial properties of the antisaccade task were identical to those of the prosaccade. The task instructions required participants to fixate the target when in the central location. They were further instructed that, as soon as the target moved to the side, they should look to the opposite location (see Figure 5-6). Participants were asked whether they had understood the task requirements; these were repeated if necessary until it was felt that participants sufficiently understood what was required of them.

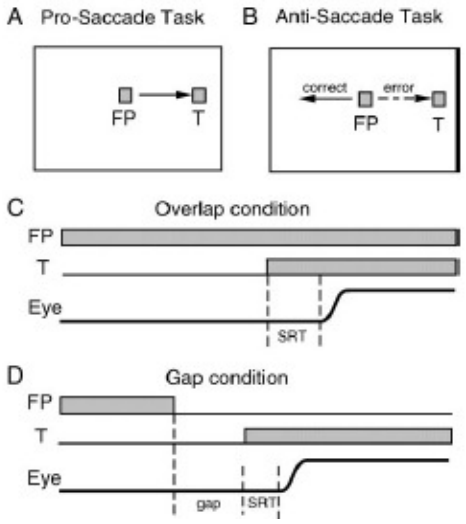
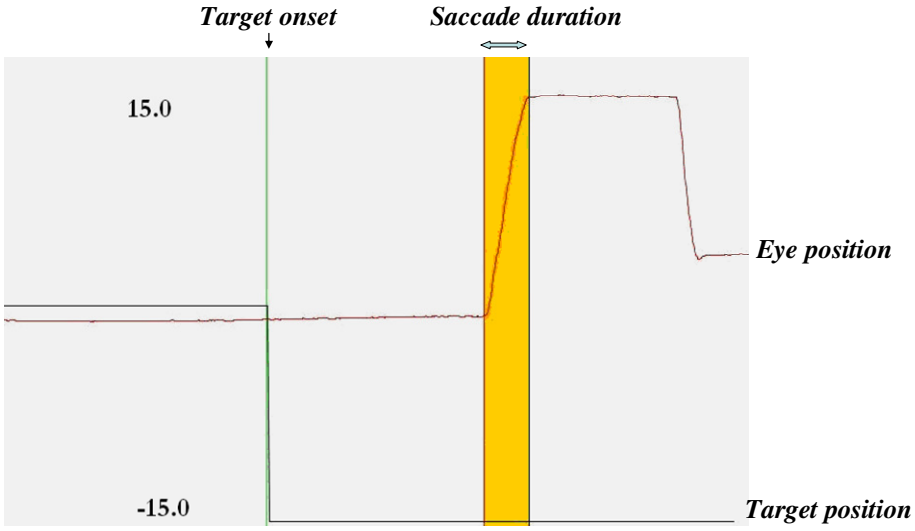


Figure 5-6: Schematic pictures of the Prosaccade and Antisaccade Tasks

(A: prosaccade task, B: antisaccade task; C: Overlap condition; D: Gap condition). FP = fixation point, T = the eccentric target, SRT = Saccadic Reaction Time. (Figure from (Munoz, et al., 2003))

Performance variables include: SRT, saccade velocity, amplitude, and directional errors, correction rate. *Gap effect*, *disengagement* and *facilitation* were also assessed for the antisaccade. Metrics of oculomotor control (i.e. saccade latency, peak velocity, and amplitude) were analyzed only for correct antisaccades, not for the error antisaccades or the corrections. Correct antisaccade (see Figure 5-7) was scored when the first saccade elicited by the individual was in the opposite direction of where the target appears.



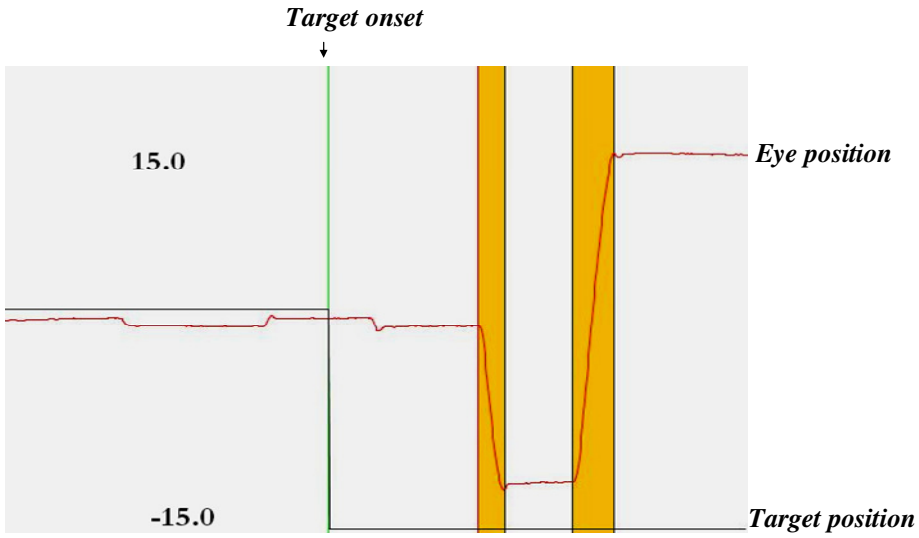
Legend: x-axis, time (ms); y-axis, degree of visual angle

Figure 5-7: An Example of a Correct Antisaccade

Antisaccade direction error was captured when the first saccade was made towards the target (see Figure 5-8). The rate of direction errors was calculated as the percentage of error trials over the total number of antisaccade trials:

$$\textit{Antisaccade error rate} = N_{Error} / N_{Total} * 100$$

In the *error trials,* if these errors were then corrected, the correction was captured as *correction rate*.



Legend: x-axis, time (ms); y-axis, degree of visual angle

Figure 5-8: An Example of an Antisaccade Error with subsequent corrective saccade

The *correction rate* is calculated as the percentage of corrective saccades over the total number of error trials. This measure can be taken as an indication of whether participants understood the task instructions and were in principle willing and able to perform the task; therefore it is a good index for response monitoring.

5.7.2.5.2 Hypotheses

Based on the previous studies, increased percentage of direction errors, less frequent corrections, increased SRT, and increased variability of SRT were predicted in the ADHD group relative to controls. It was also hypothesized that the more severe the clinical symptoms, i.e. inattention and hyperactivity/impulsivity, the greater the impairment in the antisaccade task would be.

In the ASD group, an increased percentage of direction errors and increased SRT for correct antisaccades was predicted compared to controls.

There is no study that has compared the performance of ADHD and ASD individuals directly. However, considering the fact that response inhibition has been reported to be more impaired in ADHD than ASD, it was envisaged that in the present sample the ADHD group would show more antisaccade impairments relative to the ASD group by showing a higher number of directional errors.

Moreover, no study has evaluated antisaccades in individuals with a diagnosis of comorbid ASD and ADHD. Therefore, exploratory analyses were conducted to explore whether participants in the comorbid group showed any difficulty in response inhibition compared to controls and to assess if their performance was similar to/different from the pure groups.

5.7.2.6 Data Analysis

Saccadic velocities, amplitudes, and latencies were determined by using an interactive computer analysis program that displayed each trial for review by the experimenter (the Data Viewer package; SR Research). Data recorded for each individual on each task were then evaluated on a trial-to-trial basis. The results of a saccadic analysis were stored in a tab-delimited (*.dat) output file. Output files were then opened in Microsoft Excel 2003 and copied into template files designed to extract relevant information. Template files differed between different types of eye movement paradigms. The metrics from the antisaccade and prosaccade tasks relevant to the current investigations were extracted from saccadic events by a number of Excel formulae stored in the template file. Saccadic events that were utilised for the calculation of saccadic metrics were defined according to the criteria outlined below. Saccades that did not meet these criteria were omitted from further analysis. Average measures for each participant (across saccades) were then copied into SPSS for statistical analysis.

5.7.2.7 Scoring Criteria

There is no single and universally valid scoring procedure for any of the tasks deployed here. As with the temporal and spatial characteristics of stimulus presentation in the experimental paradigms it appears that a number of different approaches exist.

Criteria for saccade analysis were set as follows in agreement with previous studies:

1) The minimum amplitude was set as *2 degrees* (after Goldberg, 2002). Saccades with amplitude lower than 2º were removed and not included for further analysis.

2) If at the target onset the eye was more than *50 pixels* off centre, the trial was excluded (after Van der Geest, 2001).

3) Only saccade latencies of greater than *70msec* were included in analyses to eliminate predictive responses that were not guided by task stimuli (after Luna, 2007).

4) Trials in which no saccadic response was made or in which the saccadic response occurred after disappearance of the target were ignored (after Van der Geest, 2001).

5) If there was a saccade or blink between *-100msec* and *+70msec* of the target onset, the trial was excluded. The first movement after *70msec* after target onset had to be a saccade whether it was directionally correct or not.

6) If there was a clear prosaccade or antisaccade contaminated by a blink, the saccade was retained but its metrices (latency, amplitude, and velocity) were removed.

For prosaccades and antisaccades analyses, as they involved the simultaneous study of two independent factor variables, factorial design was used. A repeated measure ANOVA with groups as the between-subjects factor and different conditions (Gap/Overlap/Step) as the within-subjects factor was employed to assess any interactions between groups and tasks.

5.7.2.8 Results from Prosaccade and Antisaccade Tasks

5.7.2.9 Piloting the Experiments

Both prosaccade and antisaccade were novel tasks in terms of task characteristics and were designed for the purpose of the current investigation. Therefore they were first piloted with a group of 10 healthy adults to ensure the feasibility of the tasks, i.e. to see if their instructions were easily understood, and to assess the time duration of each task when presented to the individual (including time required to calibrate the system). In the pilot study, the gap effect was observed for both prosaccade and antisaccade tasks which indicate that both tasks met the requirements of a standard gap/overlap paradigm.

5.7.2.10 Findings from the Main Study

From the total number of 120 individuals, data on prosaccade and antisaccade tasks were available for 112 individuals including 17 ASD, 35 ADHD, 38 comorbid, and 22 controls. 4 participants (2 individuals from ASD group and 2 from comorbid group) met exclusion criteria for the eye tracking tasks (see Chapter 3 section 3.2.1.2.), and 4 (2 individuals from comorbids and 2 from controls) refused to participate in these tasks.

Table 5-9 presents demographic information by group for participants who completed the prosaccade and antisaccade tasks.

No significant differences in age among the groups ($p>.05$) were observed. However, significant differences were found for FSIQ, PIQ, and VIQ (all $p<.05$). Further analysis showed that the two groups of children with ADHD symptomatology (pure ADHD and comorbid groups) had a significantly lower FSIQ, PIQ, and VIQ compared to controls (LSD post-hoc tests, $p<.05$). Moreover, the ADHD group had a significantly lower FSIQ, and VIQ (LSD post-hoc tests, $p<.05$), but not PIQ ($p>.05$), relative to the ASD group. However, no differences between the ASD and comorbid groups were observed, and the ASD group did not differ from controls in FSIQ, PIQ, and VIQ (all $p>.05$).

Table 5-9: Group descriptive for participants who completed the Prosaccade and Antisaccade Tasks: Means (SD), [Range]

	ASD (N=17)	ADHD (N=35)	Comorbid (N=38)	Controls (N=22)	$F_{(3,108)}$	P	Post-hoc LSD
Age in months	133.41 (20.77)	132.26 (31.89)	128.13 (25.18)	128.09 (29.77)	.25	.86	
[Range]	[96-168]	[84-191]	[87-200]	[91-180]			
FSIQ	113.71 (14.39)	100.69 (14.16)	106.32 (13.15)	121.27 (13.06)	11.40	<.001	Controls> ADHD, Comorbid*
[Range]	[89-139]	[70-135]	[79-142]	[102-149]			ASD>ADHD*
PIQ	108.94 (13.32)	99.00 (13.85)	105.00 (13.51)	114.73 (12.62)	6.59	<.001	Controls> ADHD, Comorbid*
[Range]	[86-136]	[64-131]	[75-141)	[100-141]			
VIQ	115.47 (16.82)	102.34 (15.89)	106.24 (14.41)	123.14 (14.76)	9.77	<.001	Controls> ADHD, Comorbid*
[Range]	[93-145]	[75-133]	[85-146]	[99-151]			ASD>ADHD*

**Post-hoc test, p<.05*

5.7.2.10.1 Group Comparisons on Prosaccade Task

Initially, analyses were conducted without adjusting for age and IQ. Group differences were explored using repeated measure ANOVA with group as the between-subjects factor and condition (Gap/Step/Overlap) as the within-subjects factor. Non-parametric tests were applied for prosaccade correction rate as it was excessively skewed and none of the transformation tests were able to normalise them. Table 5-10 shows descriptive statistics (mean and SD) on prosaccade task for the three conditions: gap, step, and overlap.

Further analysis was conducted by combining performance on the Gap/Step/Overlap measures into one mean score for each variable for each individual. The mean score was used to compute effect sizes of pairwise comparisons and compare values between groups. The results of the pairwise comparisons are shown in Table 5-11.

The groups did not differ in the number of correct trials in the prosaccade task ($F_{(3,108)}$=.92, p=.43, η^2=0.025) with the mean and SD as follows: control: mean=49.68 (5.57); ASD: mean=47.06 (8.01); ADHD: mean=47.74 (6.86); and comorbid: mean=46.58 (7.69) indicating that the clinical groups, like the control group, appeared to be willing and able to perform this task.

For saccadic reaction times (SRT), no significant between-group differences were found ($F_{(3,108)}$=1.13, p=.34, η^2=0.030). A significant condition effect was observed ($F_{(2,216)}$=218.87, p<.001, η^2=0.670) reflecting an increase in latency from gap to step to overlap conditions. No significant group by condition interaction was detected (p>.05) which indicates that the increase in latency from gap to step to overlap had a similar pattern in all groups.

Effect sizes for pairwise comparisons were calculated for saccade latency (see Table 5-11). A medium effect size of the difference was observed between ADHD and controls (d=.51) and also between ASD and control (d=.34); however, the power of these analyses was limited for a .05 two-sided level of significance (power=.44 and power=.19, respectively).

No significant between-group differences were found for RT variability ($F_{(3108)}$=1.70, p=.17, η^2=0.045). A significant condition effect was observed ($F_{(2,216)}$=77.84, p<.001, η^2=0.419) reflecting an increase in RT variability from gap to overlap. No significant group by condition interaction was detected (p>.05) which indicates that the changes in RT variability from gap to step to overlap had a similar pattern in all groups.

Analysis of peak velocity revealed a significant effect of group ($F_{(3,108)}$=3.23, p=.02, η^2=0.082). The LSD post-hoc showed a significantly higher peak velocity in the controls compared to the ASD (p=.02) and ADHD (p=.008) groups, but not the comorbid group (p=.24). Clinical groups did not differ from each other in peak velocity (all p>.05). No significant group by condition

interaction was detected (p>.05), reflecting similar pattern for saccade velocity in different conditions in all groups.

Analysis of amplitude revealed a significant effect of group ($F_{(3,108)}$=3.39, p=.02, η^2=0.086). The LSD post-hoc showed significantly higher amplitude in the control group compared to clinical groups (p=.01 for ASD, p=.004 for ADHD, and p=.03 for comorbid comparisons). Clinical groups did not differ from each other in amplitude (all p>.05). No significant group by condition interaction was detected (p>.05), which indicates that the pattern of changes in the amplitude were the same for all conditions in all groups.

Analysis of the error rate**,** showed no significant between-group differences ($F_{(3,108)}$=.77, p=.51, η^2=0.021). However, a significant effect of condition was detected reflecting a higher number of errors in gap relative to step and overlap ($F_{(2,216)}$=6.39, p=.002, η^2=0.056). No significant group by condition interaction was detected (p>.05) indicating that in all groups there was a decrease in the error rate from gap to step to overlap.

Overall, the prosaccade error rate was higher in the ASD group (mean=1.09, SD=1.52) than the other groups (ADHD: mean=.69, SD=1.54, comorbid: mean=.87, SD=1.54, and control: mean=.39, SD=1.55) though the differences did not reach statistical significance ($F_{(3,108)}$=.77, p=.51, η^2=0.021). Effect sizes for pairwise comparisons were calculated (Table 5.11): A medium effect size of the difference was observed between ASD and controls (d=.46); however, the power of this analysis was limited for a .05 two-sided level of significance (power=.29).

The prosaccade error rate was very low in all conditions and in all groups; accordingly, the correction rate was very low, and except for the prosaccade gap, further analysis could not be conducted. There was a significant group difference for prosaccade correction rate in the gap condition (Kruskal Wallis test, p=.01). The comorbid group corrected 83% of their errors as opposed to 100% in the other three groups.

The analyses for group comparisons on the prosaccade task were repeated and the effect of age and FSIQ was controlled this time using repeated measure ANOVA with age and FSIQ as covariates.

When adjusted for age, the findings did not substantially differ from the unadjusted analyses. However, when adjusted for FSIQ, the group differences became significant for prosaccade latency ($F_{(3,107)}$=2.77, p=.04, η^2=0.072) and LSD post-hoc showed that the control group was significantly faster than the ADHD group (p=.006). A significant condition effect was observed ($F_{(2,214)}$=4.00, p=.02, η^2=0.036) suggesting an increase in latency from gap to step to overlap. No significant group by condition interaction was detected (p>.05).

Moreover, when adjusted for FSIQ, the significant group effect for peak velocity disappeared ($F_{(3,107)}$=2.08, p=.11, η^2=0.055). No significant group by condition interaction was detected (p>.05).

Furthermore, both age and FSIQ were entered as covariates. This time the findings were similar to when only FSIQ was controlled for.

No between group differences were found for gap effect ($F_{(3,108)}$=1.78, p=.15, η^2=0.047), disengagement ($F_{(3,108)}$=.21, p=.89, η^2=0.006), and facilitation effect ($F_{(3,108)}$=2.54, p=.06, η^2=0.066). The result did not change after controlling for age and FSIQ.

Table 5-10: Group descriptive for participants who completed the Prosaccade Task: Means (SD)

		ASD (N=17)	ADHD (N=35)	Comorbid (N=38)	Control (N=22)
Prosaccade Latency (msec)	**Gap**	171.89 (48.45)	159.19 (36.01)	149.30 (26.20)	155.37 (30.00)
	Step	194.82 (37.29)	203.47 (32.17)	195.25 (30.63)	186.97 (39.36)
	Overlap	245.07 (55.68)	259.15 (54.08)	244.69 (55.37)	234.26 (49.85)
Prosaccade RT Variability	**Gap**	68.93(42.91)	60.30(39.03)	52.08(32.55)	54.82(39.73)
	Step	50.18(35.15)	62.23(35.91)	49.50(30.62)	44.24(20.41)
	Overlap	103.79(42.41)	112.06(40.15)	103.28(33.84)	93.21(43.53)
Prosaccade Velocity (º/s)	**Gap**	364.12 (62.69)	362.78 (61.62)	388.06 (43.17)	402.34 (62.90)
	Step	368.94 (56.05)	364.72 (52.55)	391.56 (35.54)	408.85 (67.76)
	Overlap	356.94 (52.93)	363.20 (60.52)	377.32 (36.25)	397.90 (67.51)
Prosaccade Amplitude (º)	**Gap**	13.21 (0.75)	13.09 (1.08)	13.37 (0.91)	13.78 (1.10)
	Step	13.68 (0.58)	13.65 (0. 73)	13.90 (0.75)	14.31 (1.27)
	Overlap	13.37 (0.52)	13.56 (0.76)	13.51 (0.84)	14.10 (0.94)
Prosaccade Error rate (%)	**Gap**	2.95 (3.86)	.94 (3.29)	1.33 (3.23)	.90 (3.21)
	Step	0.31 (1.28)	.47 (1.56)	.82 (4.15)	.27 (1.25)
	Overlap	0.00	.65 (2.29)	.45 (1.97)	0.00
Prosaccade Correction rate (%)	**Gap**	100	100	83.33 (40.82)	100
	Step	0.00	0.00	0.00	0.00
	Overlap	.[a]	0.00	0.00	.[a]

a. There was no data as the error rate was 0% in these groups.

Table 5-11: Effect sizes (d) of Prosaccade Task [a]

	ASD-Control	ADHD-Control	Comorbid-Control	ADHD-ASD	Comorbid-ASD	Comorbid-ADHD
Prosaccade Latency (msec)	.34	.51	.12	.11	-.22	-.37
Prosaccade RT Variability	.35	.57	.17	.14	-.21	-.42
Prosaccade Velocity (º/s)	-.65	-.65	-.33	.004	.47	.46
Prosaccade Amplitude (º)	-.77	-.69	-.52	.01	.27	.22
Prosaccade Error Rate (%)	.46	.19	.31	-.26	-.14	.12

a. Effect sizes of pairwise comparisons were calculated for the combined mean scores of gap, step, and overlap conditions.

5.7.2.10.2 Effects of Age and IQ

No significant correlation was observed for the prosaccade task variables including prosaccade reaction time and error rate with age and FSIQ across the groups (p>.05). Associations were then explored for each group which only showed a significant correlation between age and prosaccade latency in the control group (r=-.50, p=.01). Figure 5-9 depicts developmental changes in prosaccade latency in the four groups of participants. Fisher's r-to-z transformation revealed that the effect of age on prosaccade latency was greater in the control group than in the ADHD (z=1.91, p=.05) and comorbid groups (z=2.47, p=.01).

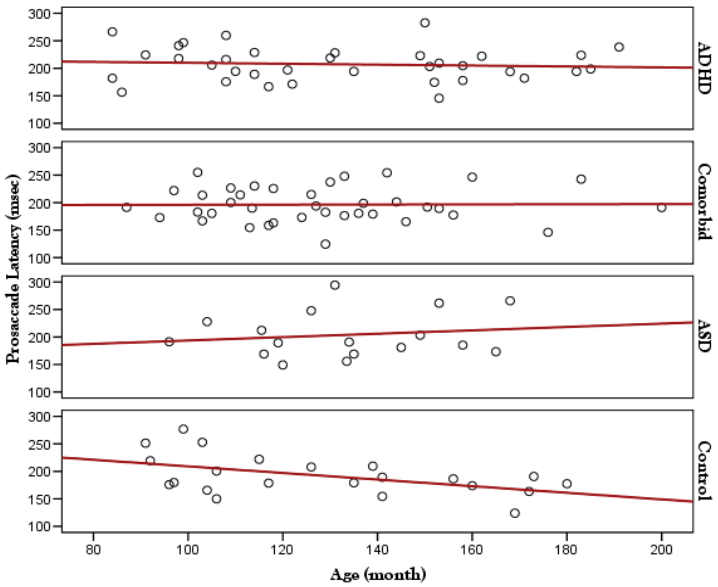


Figure 5-9: Developmental changes in Prosaccade Latency

5.7.2.10.3 Correlation between Task Measures and Clinical Measures

Correlations between prosaccade task measures and clinical measures including Conners score, SCQ and selective scores of SDQ (SDQ total score and SDQ hyperactivity) were assessed across the groups (see Table 5-12). Analysis of correlation was then conducted within each group (see Table 5-13). As the prosaccade error rate was relatively small and did not show much variance in the groups and no association was observed between the error rate and clinical measures, it is not presented in the table.

Table 5-12: Correlation between prosaccade task measures and clinical measures across all groups

	Conners Inattention	Conners Hyperactivity /Impulsivity	SCQ	SDQ Total	SDQ Hyperactivity
Latency (msec)	.09	.14	.05	.12	.14
RT Variability	.18*	.23**	.06	-.05	.79**
Velocity (º/s)	-.13	-.05	-.13	-.05	-.04
Amplitude (º)	-.19*	-.13	-.18*	-.23*	-.14
Error Rate (%)	-.09	.004	.19*	.11	.07

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level*

In the control group, a significant correlation was observed between SCQ and prosaccade latency (r=.41, p=.03) and also RT variability (r=.62, p=.001) which did not remain after controlling for age and FSIQ.

In the ASD group, there was a significant correlation between SCQ and prosaccade velocity (r=-.47, p=.03) which disappeared after controlling for age and FSIQ. In addition to the associations presented in Table 5.13, correlations between ADOS and ADI measures with the performance variables were explored in the ASD group. Significant associations were observed between the prosaccade amplitude and ADOS communication score (r=-.72, p=.001) and also between the amplitude and ADI social score (r=-.54, p=.02) indicating smaller amplitude in those with more autism symptomatology (i.e., social and communication difficulties). Correlations remained significant even after controlling for age and FSIQ.

In the ADHD group, a significant association was observed between prosaccade amplitude and Conners inattention (r_s=-.39, p=.01) and also between PACS hyperactivity and amplitude (r=-.36, p=.02) which remained significant even after controlling for age and FSIQ. These findings suggest smaller amplitude in those with more ADHD symptomatology (i.e., inattention and hyperactivity/impulsivity).

In the comorbid group, there was a positive correlation between prosaccade latency and RT variability with Conners hyperactivity (r_s=.40, p=.006 and r_s=.49, p=.001, respectively) reflecting the slower and more variable responses in those with more symptoms of hyperactivity. In addition to the associations presented in Table 5.13, correlations between ADOS, ADI, and PACS measures with the performance variables were also explored in the comorbid group. A significant association was observed between the prosaccade velocity and ADOS RRIB score (r=-.46, p=.003), indicating reduced peak velocity in those with more restricted, repetitive interests and behaviours. In addition, there was a significant correlation between PACS

hyperactivity and amplitude (r=-.41, p=.005), reflecting smaller amplitude in those with more symptoms of hyperactivity. The correlations remained significant after covarying age and FSIQ.

Table 5-13: Correlation between Prosaccade Task measures and clinical measures for each group (Unadjusted for age and FSIQ)

	Latency	RT Variability	Velocity	Amplitude
Controls				
Conners Inattention	-.006	.17	.51**	.16
Conners Hyperactivity/Impulsivity	-.16	.08	.51**	.19
SCQ	.41*	.62**	-.08	-.14
SDQ Total	.13	.13	.37	.23
SDQ Hyperactivity	-.10	.06	.34	.30
ASD				
Conners Inattention	-.19	-.16	-.15	-.03
Conners Hyperactivity/Impulsivity	.26	.29	-.22	-.01
SCQ	.34	.14	-.47*	-.37
SDQ Total	.12	-.30	-.19	-.12
SDQ Hyperactivity	.19	.10	-.21	-.58*
ADHD				
Conners Inattention	-.06	.15	-.18	-.39*
Conners Hyperactivity/Impulsivity	.12	.11	-.20	-.28
SCQ	-.01	-.05	-.11	.12
SDQ Total	-.10	-.26	.16	-.16
SDQ Hyperactivity	.18	-.24	.21	.03
Comorbid				
Conners Inattention	.13	.12	-.09	.02
Conners Hyperactivity/Impulsivity	.40**	.49**	-.16	-.04
SCQ	.00	.02	.09	-.11
SDQ Total	.48**	.46**	-.21	-.14
SDQ Hyperactivity	.10	.30	-.18	-.03

**Correlation is significant at the 0.05 level,* ***Correlation is significant at the 0.01 level*

5.7.2.10.4 Group Comparisons on Antisaccade Task

Initially, analyses were conducted without adjusting for age and IQ. Group differences were explored using repeated measure ANOVA with group as the between-subjects factor and condition (Gap/Step/Overlap) as the within-subjects factor.

Table 5-14 shows descriptive statistics (mean and SD) on the antisaccade task for three conditions: gap, step, and overlap.

Further analysis was conducted by combining performance on the Gap/Step/Overlap measures into one mean score for each variable for each individual. The mean score was used to compute effect sizes of pairwise comparisons and compare values between groups. The results of the pairwise comparisons are shown in Table 5-15.

No group differences were observed for the number of correct trials in antisaccade ($F_{(3,111)}$=1.15, p=.3, η^2=0.031) with the mean and SD as follows: control: mean=28.68 (14.80); ASD: mean=22.00 (12.21); ADHD: mean=23.14 (11.28); comorbid: mean=24.11 (12.91). However, the number of correct trials in antisaccade was significantly lower in antisaccade than prosaccade in all groups ($t_{(111)}$=19.88, p<.001), indicating the difficulty of antisaccade task for all individuals.

No significant between-group differences were found for antisaccade latency ($F_{(3,90)}$=1.27, p=.3, η^2=0.041). However there was a significant condition effect, suggesting an increase in latency from gap to step to overlap ($F_{(2,180)}$=113.09, p<.001, η^2=0.557). No significant group by condition interaction was observed (p>.05) reflecting that the increase in latency from gap to step to overlap had a similar pattern in all groups.

A medium effect size of the difference was observed between ADHD and controls (d=.41) and also between the comorbid group and controls (d=.51); however, the power of these analyses was limited for a .05 two-sided level of significance (power=.29 and power=.43, respectively).

RT variability revealed a significant main effect of group ($F_{(3,84)}$=3.24, p=.03, η^2=0.104) with the LSD post-hoc analysis revealing significantly increased RT variability in the ADHD and comorbid groups than controls (p=.006 and p=.008, respectively). As shown in Table 5-15, large effect sizes were observed between ADHD and control (d=.90) and also between the comorbid group and controls (d=.83). Moreover, a medium effect size of the difference was observed between ASD and controls (d=.51); however, the power of this analysis was limited for a .05 two-sided level of significance (power=.29).

For peak velocity, there was a significant group effect for antisaccade task ($F_{(3,90)}$=2.89, p=.04, η^2=0.088). The LSD post-hoc showed significantly higher velocity in the control group compared to ADHD (p=.02) and ASD (p=.01). No differences were detected between the control and comorbid groups (p=.33). Moreover, no significant differences were observed

between the three clinical groups (all p>.05). Neither a significant condition effect (p>.05) nor a significant group by condition interaction was detected (p>.05).

Analysis of amplitude did not reveal a significant effect of group ($F_{(3,90)}$=.90, p=.45, η^2=0.029). However, there was a significant condition effect ($F_{(2,180)}$=3.93, p=.02, η^2=0.042). No significant group by condition interaction was detected (p>.05) which indicates that the pattern of changes in the amplitude were the same for all conditions in all groups.

No significant between-group differences were obtained for the antisaccade error rate ($F_{(3,180)}$=.68, p=.56, η^2=0.019); however, a significant condition effect was detected, indicating a higher number of errors in gap relative to step and overlap conditions ($F_{(2,180)}$=32.58, p<.001, η^2=0.232). No significant group by condition interaction was detected (p>.05), which indicates that the pattern of changes in error rates was the same for all conditions in all groups. Figure 5-10 shows the antisaccade error rates for each group in each condition.

Overall, the antisaccade error rate was higher in the clinical groups (ASD: mean=54.37, SD=22.64, ADHD: mean=52.18, SD=21.85, and comorbid: mean=51.99, SD=21.21) than control group (mean=45.26, SD=23.74) though the differences did not reach statistical significance. Effect sizes for pairwise comparisons were shown in Table 5-15. A medium effect size of the difference was observed between ASD and controls (d=.39), ADHD and controls (d=.30), and also between comorbid and control groups (d=.30); however, the power of these analyses was limited for a .05 two-sided level of significance (power=.23, power=.20, and power=.19; respectively).

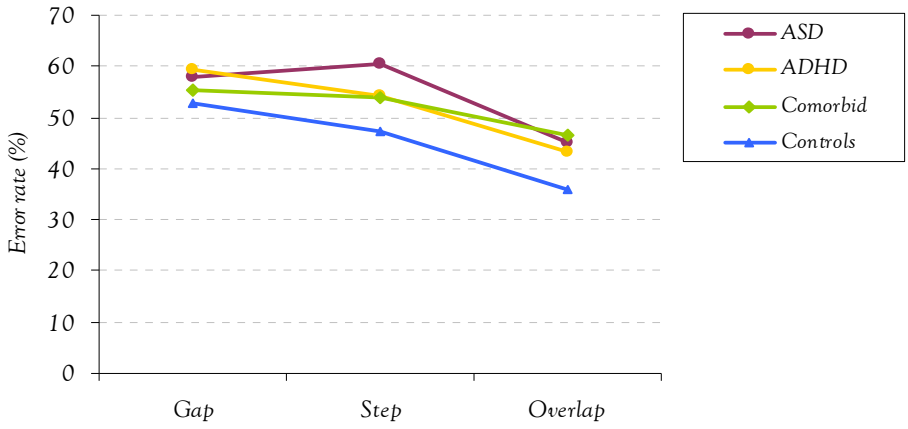


Figure 5-10: Error Rate (%) in Antisaccade Task

Analyses on the antisaccade correction rate showed a significant main effect of group ($F_{(3,103)}$=3.43, p=.02, η^2=0.091). Further analysis of this effect using an LSD post-hoc showed a significantly higher rate of correction in the control group than the ASD (p=.05), ADHD

(p=.002) and comorbid (p=.03) groups. A significant condition effect was detected indicating a higher number of corrections in gap relative to step and overlap conditions ($F_{(2,206)}$=11.19, p<.001, η^2=0.098). No significant group by condition interaction was detected (p>.05). Figure 5-11 shows the antisaccade correction rate in different groups for the different conditions.

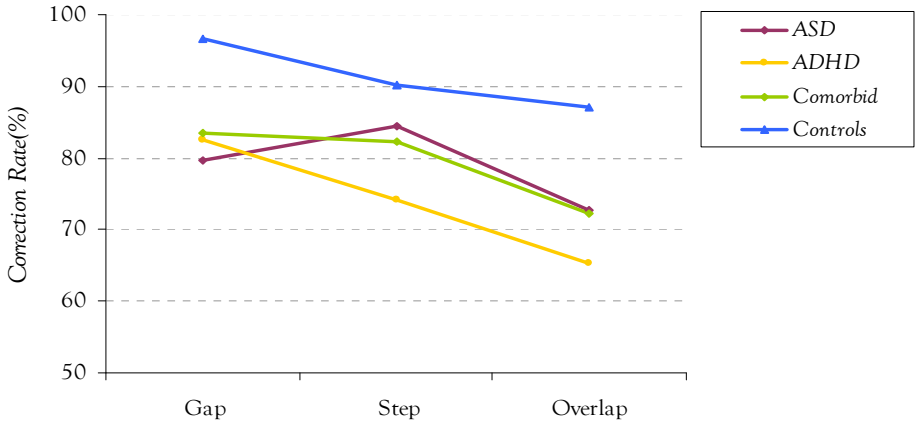


Figure 5-11: Correction Rate (%) in Antisaccade Task

The analyses for group comparisons on the antisaccade task were repeated and the effect of age and IQ was controlled this time using repeated measure ANOVA with age and FSIQ as covariates. When adjusted for age, and then separately for FSIQ, the findings did not substantially differ from the unadjusted analyses. Furthermore, both age and FSIQ were entered as covariates. Again, the findings did not differ from the unadjusted analyses.

No between group differences were found for gap effect ($F_{(3,94)}$=1.71, p=.17, η^2=0.052), disengagement ($F_{(3,94)}$=4.77, p=.31, η^2=0.042) and facilitation effect ($F_{(3,93)}$=1.00, p=.40, η^2=0.031). The findings did not differ after controlling for age and FSIQ.

Table 5-14: Group descriptive for participants who completed the Antisaccade Task: Means (SD)

		ASD (N=17)	ADHD (N=35)	Comorbid (N=38)	Control (N=22)
Antisaccade Latency (msec)	**Gap**	274.76 (96.79)	285.49 (62.32)	300.78 (63.06)	261.58 (64.27)
	Step	332.71 (59.17)	315.04 (52.41)	342.26 (72.14)	320.47 (86.82)
	Overlap	398.15 (92.58)	428.43 (114.24)	420.56 (85.47)	370.98 (87.93)
Antisaccade RT Variability	**Gap**	61.66 (29.81)	80.49 (40.01)	76.04 (43.95)	50.71 (25.10)
	Step	83.29 (51.45)	66.31 (33.27)	79.69 (46.21)	63.17 (26.90)
	Overlap	97.32 (36.99)	115.77 (38.39)	104.22 (31.24)	90.64 (34.84)
Antisaccade Velocity (º/s)	**Gap**	326.65 (62.68)	334.31 (86.21)	350.17 (51.06)	383.28 (61.18)
	Step	319.36 (66.17)	338.20 (69.46)	359.57 (52.85)	380.38 (69.31)
	Overlap	320.91 (68.55)	327.02 (89.16)	377.28 (123.22)	381.19 (73.86)
Antisaccade Amplitude (º)	**Gap**	13.76 (2.88)	13.99 (3.95)	15.29 (3.38)	14.93 (2.43)
	Step	14.14 (2.29)	14.91 (4.14)	14.90 (3.08)	15.51 (3.23)
	Overlap	13.54 (4.00)	13.06 (3.11)	14.38 (2.48)	14.75 (2.82)
Antisaccade Error Rate (%)	**Gap**	57.82 (24.50)	59.26 (24.56)	55.46 (23.05)	52.65 (24.95)
	Step	60.30 (22.85)	54.19 (23.36)	53.95 (25.12)	47.26 (23.18)
	Overlap	44.99 (28.26)	43.10 (23.04)	46.56 (24.56)	35.88 (28.23)
Antisaccade Correction Rate (%)	**Gap**	79.58 (26.36)	82.53 (22.47)	83.45 (19.09)	96.64 (5.37)
	Step	84.45 (20.35)	74.23 (24.35)	82.35 (16.40)	90.10 (11.99)
	Overlap	72.67 (32.14)	65.39 (31.71)	72.21 (27.11)	87.12 (14.92)

Table 5-15: Effect sizes (d) of Antisaccade Task [a]

	ASD-Control	ADHD-Control	Comorbid-Control	ADHD-ASD	Comorbid-ASD	Comorbid-ADHD
Antisaccade Latency (msec)	.28	.41	.52	.12	.23	.11
Antisaccade RT Variability	.51	.90	.83	.27	.23	-.04
Antisaccade Velocity (º/s)	-.85	-.64	-.29	.18	.61	.39
Antisaccade Amplitude (º)	-.34	-.37	-.01	-.02	.31	.34
Antisaccade Error Rate (%)	.39	.30	.30	-.10	-.11	-.008
Antisaccade Correction Rate (%)	.70	1.00	.90	-.24	.006	.27

a. Effect sizes of pairwise comparisons were calculated for the combined mean scores of gap, step, and overlap conditions.

5.7.2.10.5 Effects of Age and IQ

Table 5-16 and Table 5-17 show the correlations of the antisaccade task variables with age and FSIQ across the groups and by group, respectively.

Overall, across the groups antisaccade latency was moderately correlated with age (r=-.43, p<.001), indicating a faster SRT in the older participants. Moreover, in the older group, a significantly lower number of antisaccade direction errors and a higher number of corrections were observed. No significant association was observed between FSIQ and tasks variables (p>.05).

Table 5-16: Correlation between Antisaccade Task measures and age and IQ

	Latency (msec)	SRT Variability	Velocity (º/s)	Amplitude (º)	Error Rate (%)	Correction Rate (%)
Age	-.43**	-.06	-.33**	-.15	-.50**	.36**
FSIQ	.35	-.15	.09	.45	.22	.14

*** Correlation is significant at the 0.01 level*

The pattern of correlation in each group was similar to the whole sample. Again, no significant association was observed between FSIQ and tasks variables (p>.05).

Table 5-17: Correlation between Antisaccade Task measures and age by group

	Age* Latency	Age*SRT Variability	Age* Velocity	Age* Amplitude	Age* Error Rate	Age* Correction Rate
ASD	-.50*	-.03	-.14	-.15	-.44*	.56**
ADHD	-.41*	-.14	-.40*	-.25	-.64**	.54**
Comorbid	-.21	-.15	-.21	.03	-.38*	.26
Control	-.75**	-.43*	-.44*	-.25	-.56**	.42

**Correlation is significant at the 0.05 level,* ***Correlation is significant at the 0.01 level*

Figure 5-12 shows developmental changes in antisaccade latency in the four groups of participants. The correlation between age and SRT was significant indicating a faster RT in older individuals in all groups except the comorbid group. Fisher's r-to-z transformation showed that the effect of age on antisaccade latency was greater in the control group than comorbid group (z=2.59, p=.009). No differences were found between the control group and the pure groups (p>.05).

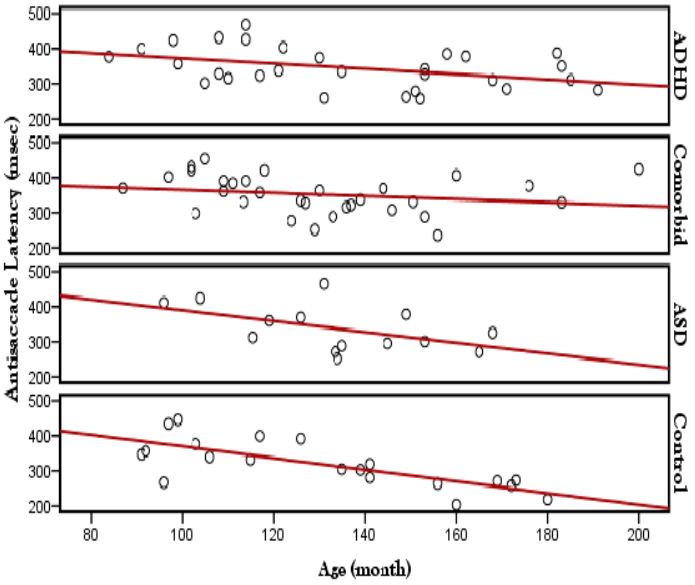


Figure 5-12: Developmental changes in Antisaccade Latency

For SRT variability, no difference in the magnitude of the correlation coefficients between the groups was detected by Fisher's *r*-to-z transformation (p>.05).

In Figure 5-13, developmental changes in antisaccade velocity in each group are shown. The correlation between age and antisaccade velocity was only significant in the ADHD and control groups. No difference in the magnitude of the correlation coefficients was detected between groups as was tested by Fisher's *r*-to-z transformation (p>.05).

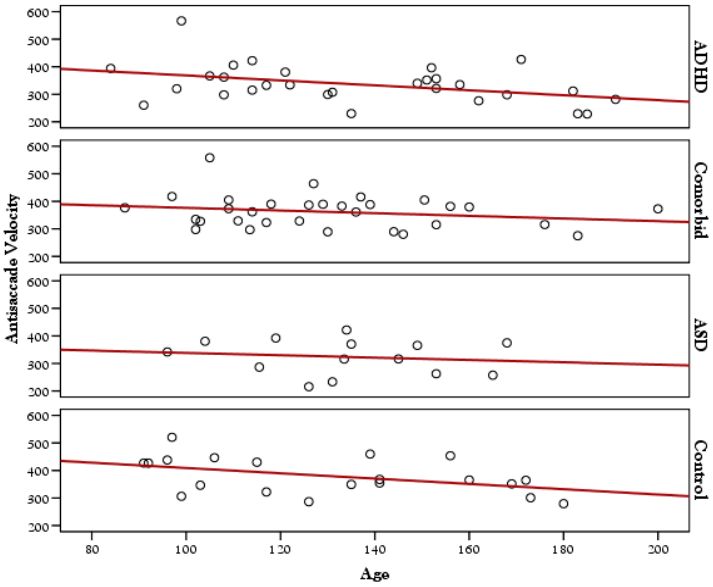


Figure 5-13: Developmental changes in Antisaccade Velocity

In Figure 5-14, the developmental changes in antisaccade direction errors are shown. The correlation was significant in all groups suggesting lower number of direction errors in older

individuals in all groups. No difference in the magnitude of the correlation coefficients between groups was detected by Fisher's *r*-to-ζ transformation (p>.05).

Finally, Figure 5-15 depicts the developmental changes in the antisaccade correction rate. No significant correlation was observed in the control group, possibly due to a ceiling effect since, in the control group, even the younger individuals were correcting their responses at the maximum level. Fisher's *r*-to-ζ transformation did not show a difference in the magnitude of the correlation coefficients between the clinical groups (p>.05).

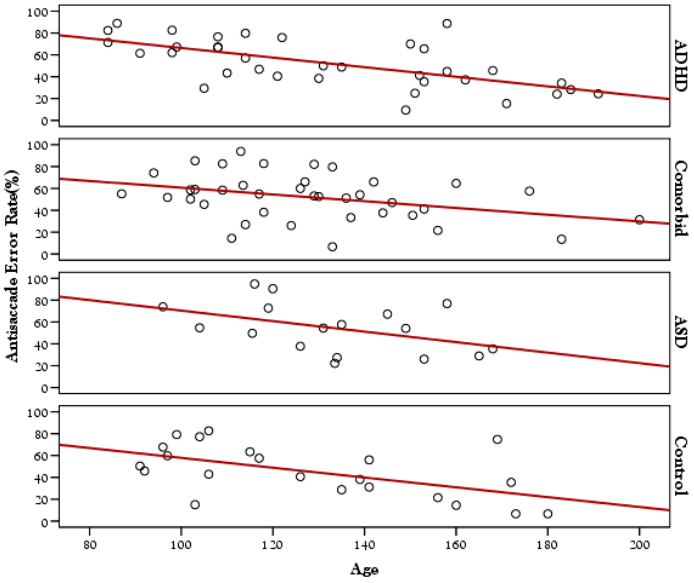


Figure 5-14: Developmental changes in Antisaccade Direction Error

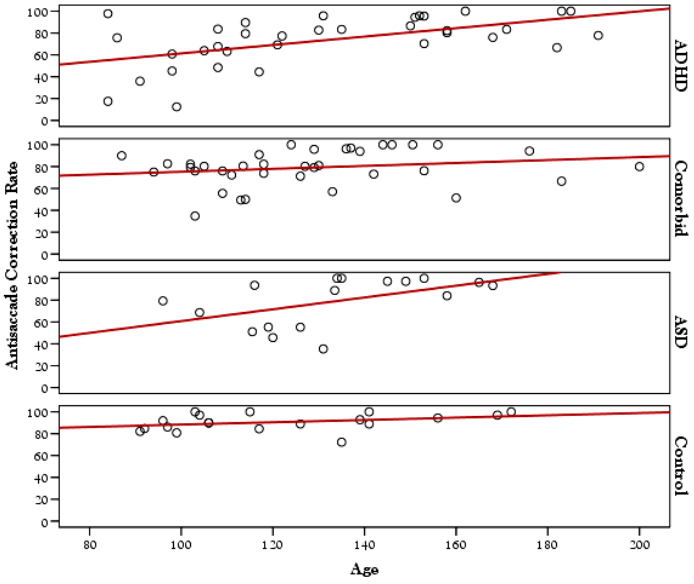


Figure 5-15: Developmental changes in Antisaccade Correction Rate

5.7.2.10.6 Correlation between Task Measures

Analysis of data pooled across all four groups revealed a significant correlation between antisaccade latency and the error rate (r=.47, p<.001) suggesting that the longer the latency the higher the error rate. Moreover significant correlations were observed between antisaccade latency and the correction rate (r=-.43, p<.001) and between antisaccade RT variability and the correction rate (r=-.22, p=.04). Finally, the error and correction rates were moderately correlated (r=-.26, p=.006). The pattern of correlation in each group was similar to the whole group (in order not to be repetitive, the statistics are not presented).

5.7.2.10.7 Correlation between Task Measures and Clinical Measures

Correlations between antisaccade task measures and clinical measures including the Conners score, SCQ and selective scores of SDQ (SDQ total score and SDQ hyperactivity) were assessed across the groups (see Table 5-18). Analysis of correlation was then conducted within each group (see Table 5-19).

Table 5-18: Correlation between antisaccade task measures and clinical measures across all groups

	Conners Inattention	**Conners Hyperactivity /Impulsivity**	**SCQ**	**SDQ Total**	**SDQ Hyperactivity**
Latency (msec)	.19*	.16	.08	.13	.26*
RT Variability	.25**	.34**	.15	.18	.24*
Velocity (º/s)	-.03	-.02	-.10	-.06	.004
Amplitude (º)	-.11	-.11	-.02	-.05	-.07
Error Rate (%)	.12	-.01	.01	.02	.04
Correction Rate (%)	-.31**	-.16	-.08	-.02	-.12

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level*

In the control group, a significant correlation was detected between SCQ and antisaccade latency (r=.39, p=.04) and also between SCQ and the correction rate (r=-.44, p=.03) suggesting slower responses and lower correction rate in those with higher SCQ. However when age and FSIQ were controlled for, the correlations were no longer significant.

The ASD group showed a significant correlation for antisaccade velocity and RRIB, as measured by ADOS (r=.67, p=.009) indicating slower saccade in those with more repetitive behaviours. The correlation remained significant after controlling for the effect of age and FSIQ.

In the ADHD group, significant correlations were observed for antisaccade latency with SDQ hyperactivity subscale (r=.44, p=.02) and Conners inattention score (r_s=.38, p=.02). Moreover, significant correlations were evident between the antisaccade error rate and PACS inattention (r=.42, p=.01) and between the antisaccade correction rate and PACS hyperactivity (r=-.40, p=.02). All these associations suggesting a poorer performance in the antisaccade task in those ADHD individuals with severe symptoms of inattention and hyperactivity. The correlations remained significant even after age and FSIQ was controlled for.

Finally, in the comorbid group, a significant correlation was detected between the Conners inattention score and correction rate (r_s=-.35, p=.02) suggesting a lower number of correction rate in those with higher levels of inattention. Conners hyperactivity/impulsivity and SCQ were both correlated with amplitude (r_s=-.31 p=.05 and r=-.480, p=.003, respectively), indicating a smaller amplitude in those with more symptoms of ADHD and ASD.

Table 5-19: Correlation between Antisaccade Task measures and clinical measures for each group (Unadjusted for age and FSIQ)

	Latency	RT Variability	Velocity	Amplitude	Error Rate	Correction Rate
Controls						
Conners Inattention	-.02	.18	.17	-.07	.09	.34
Conners Hyperactivity /Impulsivity	.09	.37	.23	-.15	.23	.21
SCQ	.39*	.19	-.29	-.03	.31	-.44*
SDQ Total	.33	.52	.29	-.40	.29	.25
SDQ Hyperactivity	.38	.28	.27	.10	.30	.21
ASD						
Conners Inattention	-.32	-.33	-.21	-.06	.12	-.05
Conners Hyperactivity /Impulsivity	.17	.42	-.19	.07	.21	-.16
SCQ	-.10	.31	-.15	.35	.11	.29
SDQ Total	.34	-.30	-.48	.43	.32	-.11
SDQ Hyperactivity	-.35	-.05	-.38	.05	.03	.35
ADHD						
Conners Inattention	.38*	.20	.04	-.15	.24	-.17
Conners Hyperactivity /Impulsivity	.18	.19	-.15	-.05	.11	.009
SCQ	.07	-.09	-.07	-.009	-.04	.11
SDQ Total	.12	.02	.16	-.12	.08	.25
SDQ Hyperactivity	.44*	.15	.12	-.17	.01	-.01
Comorbid						
Conners Inattention	.01	.06	.05	-.01	.11	-.35*
Conners Hyperactivity /Impulsivity	.02	.22	.01	-.31*	.20	.12
SCQ	-.45**	-.22	.04	-.48**	-.17	.09
SDQ Total	-.13	.07	-.41*	-.13	.10	-.11
SDQ Hyperactivity	-.08	.01	.13	-.09	-.09	-.04

**Correlation is significant at the 0.05 level,* ***Correlation is significant at the 0.01 level*

5.7.2.11 Discussion of the Prosaccade and Antisaccade Tasks

In this part of the study, saccadic eye movement parameters of three clinical groups, ASD, ADHD and a comorbid group, were compared with a group of controls. The study is the first to employ this design. Saccades were elicited under the gap, step and overlap conditions of the prosaccade and antisaccade tasks. The prosaccade task was primarily employed as a simple visuomotor task and as a baseline control condition for antisaccade to assess the ability of participants to generate saccades.

The condition effect was found in both prosaccade and antisaccade tasks as expected based on previous studies. There was an increase in SRT from the gap to step to overlap conditions, indicating that the state of attention (engaged or disengaged) influences the saccade reaction time (SRT) toward a stimulus as argued previously (Fischer & Weber, 1993).

Moreover, the proportion of direction errors was larger when the FP was extinguished prior to the cue onset (i.e. in the gap condition) than the step and overlap conditions. This is in line with previous findings which showed that a 200ms gap typically leads to an increase in the error rate as attention is not engaged any longer (Fischer & Weber, 1997; McDowell & Clementz, 1997).

5.7.2.11.1 Differences between Controls and Clinical groups in Prosaccade Task

The prosaccade task in the previous literature has yielded various and somewhat inconsistent results in ASD and ADHD groups. In the current sample, the difference in SRT between the controls and ADHD was masked due to FSIQ differences. Adjusting for FSIQ revealed that the prosaccade latency was longer in the ADHD group than the control group which is in line with previous studies (Munoz, et al., 2003). However, the group difference did not reach significance.

Similar to studies by Minshew et al. (Minshew, et al., 1999) and van der Geest (van der Geest, et al., 2001), no differences in the prosaccade latency were observed between the ASD and control groups. The same pattern of response was also observed in the comorbid group relative to controls. Even though there was a tendency for longer latency in the ASD group, the difference did not reach significance. This finding suggests that individuals with ASD have no specific problems in saccade initiation and attentional engagement. This finding is in contrast to Golberg's study on a relatively similar sample to the current study (i.e. high functioning individuals with autism with the mean age of 13.8 years) which detected slower SRT in HFA (Goldberg, et al., 2002). However, it should be noted that the study design by Goldberg was different from the current study as there was no explicit task instruction to look at the peripheral stimulus in their study. This lack of instruction might have affected the performance of ASD and control groups differently.

No significant difference was observed in RT variability in the present sample. Contrary to the expectation based on previous findings by Karatekin et al. (Karatekin, 2006; Karatekin, et al.,

2010) which reported increased RT variability in ADHD compared to controls, the difference did not reach significance in our study, even though the ADHD group showed a tendency for increased RT variability compared to controls with a medium effect size.

Some of the metrics and dynamics of oculomotor control including peak velocity and amplitude were different between the groups. Differences in peak velocity and amplitude showed the largest effect sizes between control and the clinical groups. Peak velocity was reduced and amplitude was smaller in the clinical groups. This is consistent with previous findings in ADHD (Munoz, et al., 2003) and also confirms the findings by Rosenhall et al. in ASD (Rosenhall, et al., 1988). However, it should be noted that the group differences in peak velocity might be due to differences in cognitive ability as it disappeared when the effect of FSIQ was controlled for.

The number of errors was quite small in the prosaccade task which reflects the simplicity of the task. Nevertheless the ASD group showed a higher number of errors compared to other groups but this did not reach significance. In terms of error correction, all groups except the comorbid group corrected their direction errors at the 100% level.

The gap effect was found in all groups, indicating that SRTs are influenced by the presence and removal of an initial fixation point. Deficits in the engagement of visual attention are reflected in a reduced gap effect and faster saccadic responses, whereas deficits in attentional disengagement are likely to be reflected in an increased gap effect and overall slower saccadic responses (van der Geest, et al., 2001). The present study did not find any differences between the groups in the gap effect. Moreover, disengagement and facilitation which arise for similar reasons as the gap effect did not show any group differences suggesting that all groups were equivalent in their ability to disengage, shift, and reengage visual attention. This supports the findings by Goldberg (Goldberg, et al., 2002) and Munoz (Munoz, et al., 2003) which did not find any differences in the gap effect in HFA and ADHD individuals, respectively; whereas it contradicts the study by van der Geest which reported a reduced gap effect in ASD compared to controls (van der Geest, et al., 2001).

5.7.2.11.2 Differences between Controls and Clinical groups in Antisaccade Task

Previous studies reported an increased SRT in ASD (Goldberg, et al., 2002; van der Geest, et al., 2001) and ADHD (Klein, et al., 2003; Munoz, et al., 2003) compared to controls. There was a tendency for increased SRT in both the ASD and ADHD groups with medium effect sizes in the present sample which did not establish significant differences possibly due to limited power.

The two groups with ADHD showed greater variability of saccadic RTs with largest effect sizes suggesting individuals with ADHD have difficulty with sustaining attention. This finding supports the previous studies by Karatekin et al. (Karatekin, 2006; Karatekin, et al., 2010). The

ASD group also showed a tendency for increased SRT variability but it did not reach significance.

Saccade velocity has not received much attention in previous literature on eye movements. Reduced peak velocity was observed in both ASD and ADHD groups in the present sample which is consistent with previous findings in ADHD (Munoz, et al., 2003). However, it contradicts the studies in ASD which reported no differences in antisaccade velocity in ASD compared to controls (Goldberg, et al., 2002; Minshew, et al., 1999).

Research literature to date has tended to suggest a deficit of inappropriate response inhibition in ASD and ADHD as reflected in an elevated number of antisaccade errors in these groups (Goldberg, et al., 2002; Klein, et al., 2003; Munoz, et al., 2003) (O'Driscoll, et al., 2005). Contrary to expectations, findings from the present sample failed to support this finding. Even though the antisaccade error rate was higher in the clinical groups than controls, the difference did not reach significance and the effect size of the differences were all medium. One explanation for that could be the limited power of the study to detect the group differences. A further possibility is the poor performance of the control group on the antisaccade task which is reflected in the low number of correct trials as well as a comparatively high number of antisaccade direction errors in this group (about 52% in the gap, 47% in step, and 35% in overlap conditions). This is quite a high number of errors compared to the previous studies in children which reported a relatively lower number. For example, Munoz et al. reported about approximately 40% antisaccade direction errors in their ADHD group and about approximately 27% direction errors in their control group (Munoz, et al., 2003). In another study by Mostofsky using the antisaccade task, the error rate in the ADHD group was reported as high as 59% and in controls was about 39% (Mostofsky, Lasker, Cutting, et al., 2001).

The relatively poorer performance of the control group in the current study might be partly due to fatigue as the eye movement tasks were the last test administered. However, this would likely affect all individuals independent of their group allocation. A further possibility is the behavioural profile of the control group: as it was described in sample characteristics, 13 of the control individuals who remained in the study scored above the cut-off on either domain or both domains on Conners questionnaire. Even though they did not meet the diagnostic criteria, it is still possible that their ADHD traits influenced on their task performance.

An important finding in this sample is that even though the number of errors was comparatively the same in clinical groups and controls, participants with a diagnosis of a developmental disorder (ADHD, ASD, or ASD-ADHD) failed to correct a significant proportion of their errors suggesting goal neglect and a deficit in response monitoring. This finding replicates the previous studies which showed that control participants typically correct most of their errors in the antisaccade task; however, certain clinical groups such as the ADHD (Karatekin, et al., 2010;

Klein, et al., 2003; Mostofsky, Lasker, Singer, et al., 2001; Munoz, et al., 2003; O'Driscoll, et al., 2005) or ASD (Goldberg, et al., 2002; Luna, et al., 2007; Minshew, et al., 1999) fail to do so.

This finding may suggest the involvement of anterior cingulate cortex (ACC) which has been shown previously to contribute to response monitoring by detecting errors (Carter et al., 1998; Kerns, 2006; Thakkar, et al., 2008). Thakkar, in an fMRI study, investigated response monitoring in a group of adults with ASD using an antisaccade task and found that, relative to controls, ASD participants made more antisaccade errors and showed reduced discrimination between error and correct responses in rostral ACC. Their findings demonstrated functional and structural abnormalities of the ACC in ASD that may compromise response monitoring and therefore contribute to behaviour that is rigid and repetitive rather than flexible and responsive to contingencies (Thakkar, et al., 2008).

It has been shown that people adjust their ongoing performance in behavioural tasks on a trial-to-trial basis in a number of ways, such as slowing down and being more accurate after errors. The conflict-monitoring hypothesis has been proposed to explain the behavioural adjustments. This theory posits that the dorsal anterior cingulate cortex responds to conflict and that provides a signal to recruit other brain regions such as the prefrontal cortex (PFC) to minimize conflict and improve performance (Kerns, 2006). The inability of individuals in the clinical groups to correct their responses and adjust their behaviours at the level of the control group, therefore suggests impairment in the circuit involved in response monitoring.

The two groups with ADHD had more variable saccadic RTs than controls. Furthermore, greater RT variability was related to a lower likelihood of correcting errors. This would in turn suggest that failure to correct antisaccade errors appears to be attributable to attentional fluctuations and impairments in sustaining attention on a trial-by-trial basis in clinical groups resulting from deficits in self-monitoring.

5.7.2.11.3 Differences between Clinical Groups in Prosaccade and Antisaccade Tasks

This was the first study comparing the groups with ASD and ADHD on a Gap/Overlap paradigm. Given that response inhibition was more impaired in the ADHD group, it would be expected that antisaccade performance would be more impaired relative to the ASD group. However, the study did not show any differences between the two groups. They performed relatively similarly in the baseline oculomotor measure (prosaccade task). Saccade metrics and dynamics, including velocity and amplitude, were comparatively similar in both groups on both tasks. Moreover, in the antisaccade task, which assessed response inhibition and response monitoring, the two groups showed similar performance as indexed by error and correction rates.

The comorbid group performed similarly to the pure groups in terms of generating reflexive saccade and the pattern of engagement and shift of their attention. Moreover, in a task assessing response inhibition and monitoring, their performance was to a large extent similar to the pure groups in terms of suppressing the reflexive saccades and instead generating voluntary saccades. This in turn would suggest that the pattern of saccadic eye movements of ADHD in the presence of ASD is similar to ADHD or ASD on its own.

It appeared that even though the saccadic eye movement tasks were relatively sensitive to separate individuals with a clinical diagnosis from the controls on the basis of some of the saccade metrics; it could not differentiate the clinical groups from each other. However, it is not clear whether the clinical groups had similar or different strategies for accomplishing the tasks and whether the underlying neural correlates of the eye movements are similar between the two groups.

The study also examined the relationship between task performances and clinical symptoms of participants. Across all groups, it was revealed that the symptoms of inattention and hyperactivity were related to slower and more variable saccadic responses in both tasks. In the prosaccade task, social impairment (as measured by SCQ) and inattention were associated with smaller saccade amplitude. Higher social impairment was also associated with a higher error rate in the prosaccade task and in the antisaccade task, symptoms of inattention were associated with poorer response monitoring as measured by the correction rate.

In both the pure ADHD and comorbid groups, the ADHD symptoms of inattention and hyperactivity were associated with measures of the prosaccade and antisaccade task performance such as smaller amplitude, slower saccades, and lower number of correction rate. In contrast, in the ASD group, task performance was mainly associated with autism symptomatology. Social and communication impairments in this group were related to smaller amplitude, and restricted, repetitive interests and behaviour were associated with slower responses. The comorbid group also showed an association between autism symptomatology and task measures, e.g., a higher social impairment was associated with smaller amplitude. This would therefore suggest that different factors in each group contribute to the outcome.

5.7.2.11.4 Age Effects

A further aim of the study was to explore age-related changes in task performance in line with previous studies (Goldberg, et al., 2002; Luna, et al., 2007) that considered the developmental trajectory of prosaccade and antisaccade task performance in ADHD and ASD.

Some of the tasks' measures were related to the age of the participants, albeit with different strengths. In the present sample, the age effect on prosaccade latency was only observed in the

control group and not in the clinical groups. This might suggest that the normal developmental trajectory seen in the control group was absent in the clinical groups.

Overall, developmental progression of generating voluntary saccades and saccadic suppression ability was evident in all groups in the antisaccade task. The participants in the clinical groups did show a robust developmental improvement similar to that of the control group. Antisaccade reaction times became faster and direction error became less frequent with increasing age. Also, older participants corrected their direction errors with greater frequency than younger participants. This is in accordance with previous antisaccade research which showed task improvement in older groups (Fischer, Biscaldi, et al., 1997; Klein & Foerster, 2001; Munoz, et al., 2003).

In contrast to the findings by O'Driscoll (2005) and Karatekin (2006), in ADHD (Karatekin, 2006; O'Driscoll, et al., 2005) and Luna (2007 in ASD) (Luna, et al., 2007) no differences were observed between clinical groups and controls in regards to the age effect on antisaccade direction errors and correction rate which indicates the same pattern of developmental progress in these two correlates in the clinical groups similar to the controls. The only difference in the age effect between groups was observed for antisaccade latency which was more pronounced in the control than comorbid group. This indicates that even though the performance progressed in the comorbid group in terms of initiating saccadic responses, it never reached that of the control. This could in turn suggest a delay in development rather than a deficit.

It should be noted that, as demonstrated in the figures 5.12 –5.15, there is more variation in the clinical groups compared to the controls. While the scores in the control group fall nicely along the line showing age related improvement, the scores of the clinical groups are very variable and show less of a relationship with age. It is therefore recommended that individual variation within groups is considered, as group means can hide heterogeneity, or the possibility of subgroups with different types of impairment.

Cross-sectional investigations such as the current study cannot definitively address the developmental maturation in visual attention and response inhibition and longitudinal studies are therefore needed to investigate developmental changes more in depth.

5.7.2.12 Conclusion

The current study extends previous research by comparing two groups of participants with neurodevelopmental disorders, ADHD and ASD, to a group of age-matched controls and a group of individuals with comorbid ASD-ADHD.

In the present study, the clinical groups initiated saccadic eye movements at a comparable level to the control group. No impairment in engagement and disengagement of visual attention was found in the clinical groups relative to controls. However, it was evident that the saccade

metrics like amplitude and velocity were different in the clinical groups compared to controls. Therefore, even though individuals with ASD, ADHD or comorbid ASD-ADHD could engage and disengage their attention with no difficulties, they were still not able to generate saccades with the same magnitude and speed as the controls.

An interesting finding was that even though the clinical groups did not show higher direction errors in the antisaccade task, they corrected fewer errors compared to controls, which is indicative of impairment in response monitoring, an important function of frontally driven cognitive control.

Moreover, the two groups with ADHD had more variable responses than controls in the antisaccade task and greater RT variability was related to a lower likelihood of correcting errors. This would suggest that failure to correct antisaccade errors appears to be attributable to attentional fluctuations and impairments in sustaining attention on a trial-by-trial basis in clinical groups resulting in deficits in self-monitoring.

The findings which differ in the current study from previous studies in terms of a relatively intact attentional system in individuals with ASD and ADHD could be partly due to group characteristics such as the high cognitive ability of the participants. A further explanation could be the comparatively poor performance of the control group in the antisaccade task as was detected by a small number of correct trials and also a high number of direction errors. Their poor performance might be a consequence of their ADHD traits. The lack of findings in group differences could also be explained by the lack of statistical power due to the relatively small sample size.

5.7.2.13 Limitations and Suggestions for Future Research

The present study had a number of limitations. First, the sample size, although comparable to previous studies, was relatively small and unequal. Also, the participants' age range was quite wide. Furthermore, prosaccade and antisaccade tasks were embedded in a relatively large test battery; and in order not to overburden the participants, the number of trials in each condition was kept to a minimum. A larger number of trials might ensure a more reliable assessment.

Moreover, it is suggested that future studies should focus on the saccadic eye movements of ADHD, ASD and comorbid groups using a larger sample with a narrower age range. This would hopefully give the researchers the chance to increase the number of trials in their paradigm, which in turn would increase the power to detect group differences.

Finally, the extent to which the findings on developmental changes can be interpreted and generalised remains unclear and future longitudinal studies are needed to confirm the developmental maturation in eye movement tasks.

A further suggestion would be to apply neuroimaging methods comparing ADHD and ASD in order to explore whether any differences in the neural correlate of eye movements exist between the two disorders.

5.7.3 Correlation between Two Tasks of Response Inhibition

Both Go/No-Go and antisaccade tasks have been widely used in studies of response inhibition and have been validated by showing case-control differences for ADHD and ASD.

The tasks have conceptual similarities: the Go/No-Go task is a selective motor response inhibition task where a motor response has to be either executed or not which requires the inhibition of prepotent responses (Rubia, Smith, & Taylor, 2007). The antisaccade task requires suppression of the prepotent response of looking towards a suddenly appearing visual stimulus and substitution with the novel behaviour of looking in the opposite direction. Denckla has suggested that the antisaccade task has several features which make it qualified as a pronounced test of executive function (Denckla, 1996). Therefore, it is proposed that there could be correlations between the two tasks.

In a study by Hutton et al. (2004) they investigated whether oculomotor and executive functions were related in a group of patients with first-episode schizophrenia. They observed a significant relationship between antisaccade errors and spatial working memory performance, suggesting that a shared abnormal neural substrate underlies both impairments (Hutton et al., 2004).

No study has assessed the association between oculomotor measures such as antisaccade and Go/No-Go task in ADHD or ASD groups. Given the fact that both tasks measure response inhibition, it was expected that the two tasks would show associations.

5.7.3.1 Results of Correlation between Go/No-Go and Antisaccade Tasks

Table 5-20 depicts the relationship between Go/No-Go and antisaccade tasks.

There was a significant correlation between motor RT (as measured by the Go/No-Go task) and SRT (as measured by the antisaccade task) (r=.51, p<.001). Furthermore, RT variability as measured by the Go/No-Go and antisaccade tasks were significantly correlated (r=.24, p=.03). Antisaccade error rate was correlated with commission errors (r=.25, p=.01), but not with omission errors (p>.05). RT variability in the Go/No-Go task was associated with antisaccade error rate (r=.27, p=.005) and SRT variability in antisaccade was related to commission errors (r=.26, p=.02), but not to omission errors (p>.05). Antisaccade correction rate was negatively associated with all the Go/No-Go task variables including premature responses (r=-.31, p=.001), commission errors (r=-.19, p=.05), and omission errors (r=-.36, p<.001).

Table 5-20: Correlation between Antisaccade and Go/No-Go Task Measures

Go/No-Go \ Antisaccade	Latency	SRT Variability	Error Rate (%)	Correction Rate (%)
Reaction Time	.51**	.06	.42**	-.24*
RT Variability	.43**	.24*	.27**	-.38**
Premature Responses (%)	.14	.18	.14	-.31**
Commission Errors (%)	.20	.26*	.25**	-.19*
Omission Errors (%)	.23*	.15	.19	-.36**

** Correlation is significant at the 0.05 level,* *** Correlation is significant at the 0.01 level*

5.7.3.2 Discussion

The two tests of response inhibition (i.e. Go/No-Go and antisaccade tasks) that were employed in this study were significantly correlated suggesting that both tasks are measuring overlapping cognitive mechanisms.

On Go/No-Go tasks, the group differences between ADHD and healthy controls for omission errors would indicate a sustained attention deficit whereas group differences for commission errors would indicate a response inhibition deficit (Kalff, et al., 2005). Interestingly, commission errors and not omission errors were correlated with antisaccade error rate, suggesting that commission errors and antisaccade error rates share common causes, likely involving the ability to inhibit a prepotent (oculo-)motor response. Greater RT variability, which might arise from attentional fluctuation, was related to a higher rate of commission errors and direction errors and a lower likelihood of correcting errors.

5.8 Chapter Summary

In this chapter, the executive function account was explored through administration of two tasks of response inhibition: the Go/No-Go and antisaccade tasks. Moreover, the visual attention of participants was explored at a basic level using prosaccade task.

It was found that the Go/No-Go task could differentiate individuals with ADHD from ASD and controls: the ADHD group showed deficits of response selection/inhibition by showing a higher rate of premature responses and commission errors; whereas the ASD group did not show any differences on their performance compared with controls.

The pattern of deficit in the comorbid group as revealed by the Go/No-Go task was to a large extent similar to the ADHD group which in turn would suggest that the inhibition impairment reported in ASD individuals in previous studies could be to some extent due to the unmeasured comorbid ADHD.

This was the first study comparing the groups with ASD and ADHD in prosaccade and antisaccade using a Gap/Overlap paradigm. It was found that the clinical groups initiated saccadic eye movements at a comparable level to the control group. No impairment in engagement and disengagement of visual attention was found in the clinical groups relative to controls. However, it was evident that saccade metrics like amplitude and velocity were different in the clinical groups than in the controls: smaller amplitude and reduced peak velocity were characteristics of clinical groups independent of their diagnosis. In the antisaccade task, the clinical groups did not show higher direction errors; however, they corrected fewer errors relative to controls which are indicative of impairment in response monitoring.

It was revealed that the oculomotor tasks were sensitive enough to separate individuals with a clinical diagnosis from the controls on the basis of the saccade metrics. However, it could not differentiate between the clinical groups, suggesting that this is the area in which ADHD and ASD show a cognitive overlap.

Chapter 6

Theory of Mind & Social Cognition

6.1 Chapter Overview

As mentioned in Chapter 1, Theory of Mind (ToM) and social cognition is another prominent account that attempts to explain social and communication difficulties in individuals with ASD.

In this chapter, first the literature on the three experiments that were administered in the present study (the Triangle Task, Strange Stories, and a task of social vs. non-social cueing) will be briefly reviewed. Subsequently, the findings from each experiment will be discussed.

6.2 Theory of Mind (ToM)

The term 'theory of mind' was introduced by Premack and Woodruff (1978) to describe the ability to attribute mental states to oneself and others in order to explain and predict the behaviour of others based on their mental states (Premack & Woodruff, 1978). The ToM account hypothesises that there is a failure of the innate system for attending to and representing mental states, such as intentions, feelings, beliefs, and desires to oneself or others and, as a consequence, have difficulties in social interaction and communication (Baron-Cohen, et al., 1985).

ToM functioning has been assessed at different levels: First-order false belief tasks involve inferring a person's own mental state, while second-order false belief tasks involve being able to 'mentalise' people's mental states (Baron-Cohen, 2000). In false belief tasks, the subject must follow a character's mistaken mental state in order to predict behaviour based on that belief (in contrast to reality or the subject's own belief).

Even though, studies on children with HFA or Asperger's disorder have shown impairment in first and/or second order ToM functioning (Baron-Cohen, 2000; Frith, 1989b; Happe, 1994a; Leslie & Frith, 1987), some studies in adults or older autistic children with high verbal abilities show no impairment (Bowler, 1992; Ozonoff, Pennington, et al., 1991).

It has been suggested that normal intellectual and, in particular, verbal abilities scaffold ToM abilities, since, by the end of childhood, many individuals with autism show ToM competencies, at least in structured and verbally mediated situations (Bowler, 1992). However, a recent study by Klin challenged this view and showed that the level of social adaptive behaviour in HFA individuals lagged behind expectations based on their cognitive potential (Klin et al., 2007).

Regardless of these studies, passing the ToM tasks does not necessarily imply that these individuals are able to function adequately in social situations, since in daily life social information is more subtle and difficult to interpret (Spek, Scholte, & Van Berckelaer-Onnes,

2010). Frith suggested that their success in ToM tasks could be seen not as proof of ToM ability but rather as evidence that they are able to 'hack out' some strategy for solving the tasks (Frith, Morton, & Leslie, 1991).

To address this debate, some researchers have introduced 'advanced theory of mind' tasks such as Strange Stories (Happe, 1994a), Triangle animations (Abell, Happe F., & U., 2000) and Baron-Cohen et al.'s Reading the Mind in the Eyes Test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) to assess participants in more complex and naturalistic social situations in the hope that these situations would challenge their ToM ability more than previous, simplified tasks and provide a better measure of the ability to function in social situations.

6.3 Theory of Mind & Social Cognition in ASD versus ADHD

It has been shown that individuals with ADHD also exhibit behavioural difficulties with social interaction (Buhler, Bachmann, Goyert, Heinzel-Gutenbrunner, & Kamp-Becker, 2011; Clark, et al., 1999; Fine, Semrud-Clikeman, Butcher, & Walkowiak, 2008; Santosh & Mijovic, 2004), though it is unclear whether their problems arise from substrates similar to those with ASD. Santosh and Mijovic used the term 'autistic-like' to describe the social and communication difficulties (SCD) of a group of children with ADHD. They reported that in their sample of children and adolescents with ADHD-Combined type, SCD was associated with speech and language difficulties, repetitive behaviours, developmental difficulties, affective symptoms, conduct problems and ADHD symptoms (Santosh & Mijovic, 2004).

Buitelaar et al., in a direct comparison of children with ASD and ADHD on a range of first- and second-order ToM tasks as well as an emotion recognition task, revealed impaired performance in both groups and showed that groups could not be differentiated from each other on the basis of the ToM tasks. The authors suggested that mentalising difficulties in individuals with ADHD may be related to their executive difficulties (Buitelaar, van der Wees, Swaab-Barneveld, & van der Gaag, 1999).

However, Sodian and Hu¨lsken in a theoretical approach outlined the possibility of a difference in the development of ToM-deficits in ASD and ADHD groups. They suggested that while children with ASD show ToM deficits from an early age (Jones & Klin, 2009); children with ADHD are assumed to develop the deficit in relation to their difficulties in inhibitory control. They proposed that contrary to children with ASD, there is no primary deficit in ToM abilities of individuals with ADHD but the deficits develop in the course of the inhibitory deficit (Sodian & Hu¨lsken, 2005).

Fine et al. in a study compared a group of children and adolescents with ADHD (N=37, mean FSIQ=107.87), ASD (N=30, mean FSIQ=104.16) and controls (N=19, mean FSIQ=116.47) on a measure of social perception called The Child and Adolescent Social Perception Measure

(CASP). They assessed participants in their ability to interpret nonverbal social information from video vignettes of emotionally charged interactions and found significant between group differences in recognition of emotions on video as the control group performed better than both clinical groups. The number of inattention symptoms was reported to be a significant contributor to poorer video interpretation across diagnostic groups (Fine, et al., 2008).

In a recent study by Buhler et al. (2011), a large sample of ASD (N=86, mean FSIQ=105.4), ADHD (N=84, mean FSIQ=97.9) and comorbid (N=52, mean FSIQ=99.0) groups in the age range of 5–22 years were compared on a test battery consisting of Test battery for attention performance (TAP), Facial Emotion Matching (FEM), and Social Attribution Task (SAT). They reported that the two groups with ADHD showed more impaired inhibitory control than the ASD-group, however, no significant differences were observed between the groups in two ToM tasks. They further divided their participants in two group (age<10y and age≥10y) and interestingly found a significant difference between the younger children, i.e. better performance in ADHD group, but not among the older children regarding the amount of mistakes in the FEM. They concluded that children with ADHD develop deficits in ToM as they become older (Buhler, et al., 2011). Their finding was in agreement with the theoretical model and preliminary findings on the relation between a deficient inhibitory control and deficits in ToM outlined earlier (Sodian & Hu¨lsken, 2005).

6.4 Neural Substrates of Theory of Mind & Social Cognition

Neural correlates of ToM have been well studied using functional brain imaging. Fletcher et al. (1995), in a PET study compared the brain regions activated during reading and answering questions about stories involving complex mental states (ToM stories) and those involving inferences of physical cause and effect (physical stories). They found a specific pattern of activation associated with mental state attribution: increased activation in the medial frontal gyrus on the left (Brodmann's area 8), as well as in the posterior cingulate cortex and the right inferior parietal cortex (BA 40) at the temporoparietal junction, was observed during the ToM stories involving mentalising task (Fletcher et al., 1995)

In another study by Gallagher et al. (2000), in which the same set of stories as in Fletcher's was used in an fMRI study with normal volunteers. In addition, participants were shown figurative drawings (humorous cartoons) which similarly prompted attribution of mental states. They found greater activation during ToM stories and cartoons in areas similar to those found by Fletcher including Brodmann areas 8/9 and the border of 10 and 32. These areas relate to the paracingulate sulcus. Activity was also observed in the temporoparietal junction bilaterally (Gallagher et al., 2000).

The ToM network has been identified across a range of studies using ToM tasks such as a set of stories about false beliefs and false photographs. The brain regions in this network are consisted

of: right and left temporoparietal junction (RTPJ/LTPJ), superior temporal sulcus (STS), precuneus (PC) and medial prefrontal cortex (MPFC) (Kliemann, Young, Scholz, & Saxe, 2008; Saxe & Powell, 2006; Saxe & Wexler, 2005).

Behavioural and neuroimaging studies have suggested that individuals with ASD show diminished attention to social cues when observing social situations (Klin, Jones, Schultz, Volkmar, & Cohen, 2002a, 2002b), are less likely to use ToM capacities to spontaneously attribute social meaning (Klin, 2000), and appear to use atypical (and to some extent compensatory) strategies to recognize faces and facial expressions of emotions (Hobson, Ousten, & Lee, 1988).

6.5 Triangle Task

The Triangle Task is a set of animations designed by Abell et al. (2000), based on the original animations of Heider and Simmel (Heider & Simmel, 1944). The animations in the original design could be described in terms of a goal-directed (G-D) action (like chasing and blocking) and they were not intended to attract mental state attribution (like bluffing or deception) with their motion properties.

Heider and Simmel (1944) demonstrated that viewers consistently attributed personality traits and emotions to films of geometric figures, regardless of what instructions they were given.

The triangle animations modified by Abell et al. (2000) consist of three novel sets of geometric animations representing three different types of motion: random movement, G-D interactions, and ToM interactions. The random set is intended to illustrate purposeless movement and no interaction between two triangles; G-D animations are intended to depict an interaction consequent upon the physical action or behaviour of one of the triangles; and the ToM animations are intended to depict an interaction involving one triangle reacting to the other's mental state (Abell, et al., 2000).

6.5.1 Triangle Task Performance in ASD

In the first experiment by Abell et al., ten triangle animations were selected from three conditions: two from the Random condition and four animations each in the G-D and ToM conditions. The animations were shown to four groups: children with autism (N=15, mean age=12.10 years), children with moderate learning disabilities (MLD, N=17, mean age=13.8 years), normally developing 8-year-olds (N=15), who were matched on verbal mental age with the two clinical groups and a group of adults (N=14). No differences in the use of mentalising terms were found between the groups; however, they found that children with autism produced fewer appropriate mentalising responses. Children in the autism group often referred to a mental state that did not fit with the respective ToM animations. They reported that even those autistic individuals who had passed first- and second-order false belief tasks performed poorly

on the triangle animations. This would suggest that, for individuals with ASD, passing false belief tasks do not necessarily signal the intuitive ability to attribute mental states appropriately in real time (Abell, et al., 2000).

Castelli et al. (2002) used the Triangle Task in a group of adults with Asperger's disorder (N=10, mean age=33 years). They used four different examples of three different animations: Random, G-D, and ToM and found that the group with Asperger's disorder produced fewer and less appropriate mental state descriptions, and more inappropriate or inaccurate mental state descriptions than a comparison group matched for verbal and non-verbal abilities (Castelli, Frith, Happe, & Frith, 2002).

Salter et al. (2008) used a large sample of children and adolescents with ASD aged 6 to 18 years (N=56, mean age=10.37 y, mean VIQ=98.89) and compared them with 56 age, sex and IQ-matched controls on the Triangle Task. In this large, carefully controlled study, they did not find substantial differences between the groups in term of their use of mentalising language. The only significant difference which emerged between the groups was on the measure of appropriateness. Their ASD children did not use significantly less mentalising language in terms of intentionality, even though their scores in this dimension were lower than controls. Moreover, they asserted that this difference in appropriateness of response was not clearly related to verbal ability in the ASD group. Contrary to their expectations, the authors did not observe a strong correlation between the Triangle Task performance and autistic behaviours; therefore, this raised questions as to the external validity of the task in terms of measuring everyday social functioning (Salter, Seigal, Claxton, Lawrence, & Skuse, 2008).

6.5.2 Neuroimaging Studies Using the Triangle Task

Castelli et al. (2000) scanned 6 healthy adults to examine brain activation during triangle animations and showed increased activation in a network of brain regions, including the medial prefrontal cortex, the temporal pole adjacent to the amygdala region and the temporoparietal junction. As the two important brain regions they found to be involved, the paracingulate sulcus and temporoparietal junction, showed overlap with studies of self monitoring and perception of biological motion, the authors suggested that the ability to make inferences about other people's mental states likely evolved from the ability to make inferences about others' actions and movements (Castelli, et al., 2000).

6.6 Strange Stories

The Strange Stories test is a set of short vignettes designed by Happé in 1994 (Happe, 1994a) as an advanced test of ToM. Participants read stories and are asked to explain why a character says something that is not literally true. In order to perform well on this task, one must attribute of mental states such as desires, beliefs or intentions to the characters.

The stories are not imaginative or highly fictional. They are simple accounts of events, which concern the different motivations that can lie behind everyday utterances that are not literally true.

Happé originally designed 24 mentalising stories with a set of six control stories requiring understanding of physical states. The mental state stories involved items such as a double bluff, pretence, a lie, a white lie, persuasion, forgetting, appearance/reality, a joke, irony, and misunderstanding. The physical stories were constructed to parallel the mental state stories in requiring inference beyond the information stated, but they did not require or invite consideration of their mental states.

Both types of stories involved people and required the integration of information from the constituent sentences into a story structure as well as having to remember and link events and to infer an implicit element.

The control stories used in the original study by Happé were not equated for difficulty with the ToM stories and the results showed that all participants performed at ceiling on the control stories (Happe, 1994a). Later, Fletcher et al. (1995) modified the control stories by creating new physical stories which were matched to the mental state set in terms of difficulty. They also introduced a new control task called 'unlinked sentences' where participants were required to recall a specific fact from one sentence. 'Unlinked sentences' contrasts with both story types in not requiring integration of material into a story structure, and not requiring inference. However, it did require, in common with the other conditions, reading, attention to sentence meaning, and memory (Fletcher, et al., 1995).

6.6.1 Strange Stories Performance in ASD

In the first study using Strange Stories, Happé compared 18 individuals with autism (mean age=20.6 years) with three different control groups: 1) 11 individuals with mental handicap (mean age=19.4 years), 2) 26 control children (mean age=8.6 years), and 3) 10 control adults (mean age=20.5 years). They recruited participants of differential ToM abilities: of those 18 individuals with autism, 12 had passed the first or second order ToM tasks and 6 did not and were classified as the 'no-ToM' group. The no-ToM group performed worse than those who passed either first or second -order ToM. However, even the ToM passers had difficulty in the Strange Stories test and what distinguished them from the controls was not a failure to use mental state terms, but a failure to use the context-appropriate terms.

They also found that the individuals with a mental handicap who matched the 'no-ToM' group on verbal IQ, performed significantly better than this group on the Strange Stories; so the authors concluded that the group differences found may be due to real underlying differences in understanding of mental states, that is, ToM capabilities (Happe, 1994a).

It seems that even relatively able individuals with ASD have difficulties appreciating non-literal speech, such as irony, jokes, white lies, metaphorical expressions, and indirect requests. Jolliffe and Baron-Cohen assessed adults with HFA and Asperger's disorder using Strange Stories and found that they could provide mental state answers, but had difficulty in providing contextually appropriate mental state answers (Jolliffe & Baron-Cohen, 1999a). This finding was replicated in a study by Brent et al. (2004) and later by Kaland et al. (2005) in children and adolescents with HFA and Asperger's disorder (Brent, Rios, Happe, & Charman, 2004; Kaland et al., 2005).

White et al. recently (2009) compared 45 children with ASD (mean age=9.24 years, mean VIQ=111) to 27 age, gender, PIQ, and VIQ-matched controls (mean age=9.48 years, mean VIQ=115) using a standard ToM battery and a modified version of Strange Stories. They included eight mental state stories, eight physical state stories (they referred to those as human-physical stories), and eight passages of unlinked sentences. They also created two new sets of physical stories: eight animal-physical stories and eight nature-physical stories.

All the physical stories were matched to the mental state stories for difficulty. Children with ASD who showed ToM impairment in standard ToM battery, performed significantly more poorly than controls solely on the mental, human-physical, and animal-physical stories with greatest impairment on the former and least on the latter two. Therefore, the authors concluded that a mentalising deficit may affect understanding of biologic agents even when this does not explicitly require understanding others' mental states (White, Hill, Happe, & Frith, 2009).

6.6.2 Strange Stories Performance in ADHD

Charman et al. (2001) explored the ToM ability of a group of boys with ADHD (N=22, mean age=8 years and 7 months) compared with a group of age-matched controls (N=22). They used 12 vignettes of Strange Stories and found no differences between the two groups (Charman, Carroll, & Sturge, 2001).

6.6.3 Neuroimaging Studies Using Strange Stories

Fletcher et al. (1995), in a functional brain imaging study using PET, assessed the performance of six healthy individuals in a subset of the eight mental state stories, eight physical stories which were of comparable difficulty to those of the mental state, and eight unlinked sentences.

They showed that the attribution of mental states is particularly associated with the function of a highly circumscribed brain system. They observed that both story conditions, when compared to the unlinked sentences, showed increased activation in the following regions: the temporal poles bilaterally, the left superior temporal gyrus and the posterior cingulate cortex. Comparison of the mental state stories with physical stories revealed areas uniquely activated during mental state attribution: it was only this task which produced activation in the medial frontal gyrus on the left (Brodmann's area 8), together with a portion of the posterior cingulate cortex (Fletcher,

et al., 1995). These areas have been shown to be activated in previous PET studies involving verbal memory, language and story comprehension (Mazoyer et al., 1993).

Later, Happé et al. (1996) adopted the same set of stories as Fletcher et al. (1995) used to assess the neural correlates of ToM in five adults with Asperger's disorder. They found that all individuals with Asperger's succeeded in correctly answering most of the test questions from the mentalising stories. They found that like the previous study in healthy adults by Fletcher et al., the same areas were activated in the Asperger's volunteers when comparing the story condition to non-story (i.e. the unlinked sentences): the temporal poles bilaterally and the left superior temporal gyrus. However, this time, the difference between stories and sentences was significantly less pronounced in all regions. The authors suggested that individuals with Asperger's disorder process meaningful connected narrative and meaningless jumbled sentences in a more similar way than do controls. Moreover, comparison of the mental state stories with physical stories revealed a critical difference between the clinical and control groups: the Asperger's group did not show activation of the medial part of left prefrontal area (Brodmann's area 8) during ToM stories (Happe et al., 1996).

6.7 Gaze Perception and Gaze-following Behaviours

Information gained from another person's eyes plays a crucial role in social interaction and communication. Among various functions of gaze processing, detection of gaze direction provides information about the gazer's intention, direction of attention and emotional and mental states.

There is a well-established evolution in the use of gaze over the first 5 years in typical development that parallels or scaffolds the emergence of other social cognitive abilities, including face processing, gender discrimination, identity recognition, facial expression discrimination, joint attention and ToM (Itier & Batty, 2009). For the purpose of the current study, an overview on orienting of attention by gaze will be presented.

A strong sensitivity to eye gaze direction has been observed from early days in life. Previous studies have shown that neonates prefer to look at faces with eyes open rather than eyes closed (Batki, Baron-Cohen, Wheelwright, Connellan, & Ahluwalia, 2000) and they look longer at faces with direct gaze rather than averted gaze (Farroni, Csibra, Simion, & Johnson, 2002). There is evidence that by 4 months, infants can discriminate gaze direction (Caron, Caron, Roberts, & Brooks, 1997; Hains & Muir, 1996) and this sensitivity to direct gaze modulates face recognition in early infancy (Farroni, Massaccesi, Menon, & Johnson, 2007).

Detecting the eye gaze direction affects gaze-following behaviours such as joint attention. It has been shown that by 6 months, babies can orient their attention to an object being looked at by

another person (Morales, Mundy, & Rojas, 1998); and by 9–10 months, they are able to follow head-turn and gaze shifts spontaneously (Butterworth & Jarrett, 1991; Corkum & Moore, 1998).

For individuals with ASD, the available evidence suggests otherwise. Disruptions of typical engagement with other people, reduced interaction with others, less interest in looking at faces, in particular the eye region (Dalton et al., 2005; Klin, et al., 2002b), have been well documented in ASD. While typically developing children detect direct gaze quicker than averted gaze, children with ASD respond similarly to both gaze types and do not seem to have preferential sensitivity to direct gaze (Senju, Tojo, Yaguchi, & Hasegawa, 2005; Senju, Yaguchi, Tojo, & Hasegawa, 2003).

A deficit in the development of joint visual attention is one of the earliest behavioural manifestations of ASD, and it is thought to compromise opportunities for social learning and subsequent social and communication development (Baron-Cohen et al., 1996; Mundy & Burnette, 2005). The reason that children with ASD fail to develop joint visual attention might be due to the difficulty they have in shifting their gaze and, therefore, their attention in the direction of another person's eye gaze (Senju, Tojo, Dairoku, & Hasegawa, 2004).

6.7.1 Gaze Cueing and Orienting of Attention

Orienting of attention (overtly, through eye movements or head turns, or covertly through a shift of spatial attention) to the direction of another's gaze has been the studied extensively. The attentional mechanism process corresponding to joint visual attention ability, or reflexive orienting towards the direction of other's eye gaze, was directly assessed using a traditional cueing paradigm: Posner-style spatial cueing paradigm, 1980 (Posner, 1980). In cueing paradigms, participants are asked to detect visual targets, which may appear on either side of a visual fixation point. Before the target appears, a stimulus cues the participant to one side or the other.

Orienting of attention is controlled in two major ways: (a) Exogenous (bottom-up, reflexive, or stimulus driven) orienting which is thought to 'automatically' move attention rapidly (within 150 ms) to the location of a visual cue in the periphery, and (b) Endogenous (top-down, voluntary, or goal driven) orienting which is thought to 'voluntarily' redirect attention to a place where something is expected to occur.

Traditionally, exogenous control is achieved by orienting attention to events such as a sudden change in luminance, texture, or motion in the visual field, often in the periphery as used in the basic peripheral cueing paradigm by Posner and Cohen (Posner & Cohen, 1984). In Posner and Cohen's study, two empty boxes were presented to the left and right of the central fixation point. The outline of one of the boxes was then briefly brightened before a target appeared randomly in either box after variable cue-target stimulus onset asynchronies (SOAs). The

participants were instructed to respond by pressing a key as soon as the target was detected (see Figure 6-1, Panel A).

Faster reaction time and/or more accurate performance to the targets in the cued location compared with those in the un-cued location indicate attention shifts to the cued location (Frischen, Bayliss, & Tipper, 2007). The difference in reaction time (RT) for detecting targets at cued versus un-cued locations provides an index called 'cueing effect' which has been shown to occur even when the cue is not predictive of the target location. Furthermore, it has been observed that instructions to ignore the cue fail to disrupt the cueing effect (Jonides, 1981; Remington, Johnston, & Yantis, 1992). Thus, this kind of orienting is considered automatic and reflexive because it cannot be suppressed.

Endogenous control has been studied by Posner type cueing paradigms using a centrally, rather than peripherally, presented cue. Such cues may be an arrow pointing to one direction (see Figure 6-1, Panel B) or other cues such as a schematic face looking to the left or right. In a study by Jonides in 1981, an arrow was presented as a central cue. He found no evidence for rapid attention shifts to the cued location when the cue was non-predictive of the target location (i.e. when the central cue validly cues the target location for only 50% of trials) (Jonides, 1981). However, more recent studies showed otherwise; they observed cueing effect even with spatially non-predictive central cues (Friesen & Kingstone, 1998; Ristic, Friesen, & Kingstone, 2002; Tipples, 2002).

For studying the precise cognitive mechanisms underlying orienting of attention in response to observed eye-gaze direction, modifications of Posner's cueing paradigm have been used (Friesen & Kingstone, 1998; Ristic, et al., 2002).

For example, Friesen and Kingstone explored whether observed gaze shifts produce orienting responses in adults. Participants were asked to detect a target which appeared either to the left or the right of a schematic face after the pupils of the face appeared, constituting a directional gaze cue. They were explicitly informed that the direction in which the eyes were looking was not predictive of the target location. The authors observed the cueing effect which emerged relatively rapidly at short cue-target SOAs even when the cue was uninformative and disappeared with longer SOAs (1,005ms). Thus, they suggested that the tendency to move attention to the location of another person's eye gaze is reflexive and not dependent on the recruitment of voluntary attention and this reflexive orienting is unique to biologically relevant stimuli (Friesen & Kingstone, 1998). However, Tipples reported the cueing effect in response to a non-social cue such as an arrow, even when cue direction was uninformative, and therefore suggested that an arrow can evoke the same reflexive orienting effect as eye gaze cues in adults (Tipples, 2002).

Moreover, Ristic et al. showed RT facilitation at the cued location for both eye gaze and arrow cues in adults (N=19) and preschoolers (N=19, aged from 3-5 years), and suggested that gaze cues are not special but serve as a simple spatial cue, just as the direction of an arrowhead does. The only difference between the two cues was the longer RTs for arrows than for eyes, reflecting perhaps that gaze is more alerting than an arrow in typically developing group (Ristic, et al., 2002).

However, as Ristic et al. reported in their experiment 3, data from a split-brain patient argued against the conclusion that eyes are not special. The split-brain patient showed reflexive orienting to the eye gaze cue only when stimuli were presented to the right hemisphere, the hemisphere associated with face processing. In contrast, arrow cues elicited reflexive orienting regardless of which hemisphere stimuli were presented to. The authors concluded that 'eyes are special', as it seems that qualitatively different mechanisms subserve the processing of biological or social stimuli compared with non-biological or non-social stimuli (Ristic, et al., 2002).

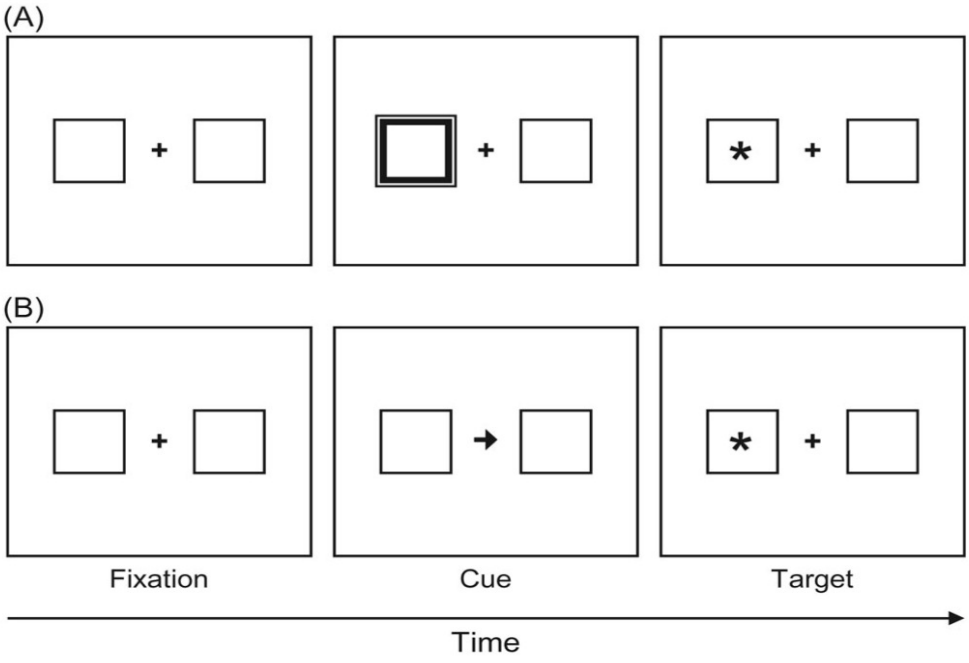


Figure 6-1: Basic spatial cueing paradigm, using a peripheral sudden-onset cue (Panel A) or a central symbolic cue (Panel B).

In Panel A, the target appears in the previously cued location (valid trial), whereas Panel B shows an invalid trial in which the target appears in the un-cued location (Figure from (Frischen, et al., 2007)).

Although Posner's attentional cueing paradigm is an artificial experimental setting, it allows for a detailed investigation of people's sensitivity to eye gaze cues by measuring the efficiency of reflexive orienting under highly controlled conditions (Nation & Penny, 2008).

6.7.2 Neural Correlates of Gaze Cueing and Orienting of Attention

Different neural systems appear to be specialised in exogenous and endogenous control of attention. Frischen et al. reviewed in details the neural correlates of gaze perception (Frischen, et al., 2007). A selective review will be presented here.

Exogenous orienting is assumed to be subserved by a posterior attention system involving subcortical structures such as the pulvinar and the superior colliculus (SC) (Posner, Cohen, & Rafal, 1982; Rafal, Calabresi, Brennan, & Sciolto, 1989), whereas endogenous orienting is presumably supported more strongly by cortical areas in anterior (e.g., the cingulate gyrus and the supplementary motor area, which are involved in executive functions; (Corbetta, Miezin, Shulman, & Petersen, 1993)) and posterior regions of the brain (e.g., intraparietal sulcus; (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000)).

The human brain region that is responsive to perceived gaze direction is the STS area, with both dynamic (Hooker et al., 2003) and static face displays (Hoffman & Haxby, 2000). The STS is also heavily connected with the parietal cortex, which is implicated in orienting of attention (Harries, Perrett, & Lavender, 1991).

6.7.3 Gaze Cueing and Orienting of Attention in ASD

Evidence for impairment in gaze following behaviours in ASD is based on studies involving interpersonal interactions within real world experimental paradigms; however attentional orienting in response to gaze cues has been often investigated using a Posner's type cueing paradigm. For the purpose of this study, only those studies who applied Posner's Cueing paradigm in ASD group will be reviewed.

Although it is well established that people with ASD have difficulty following gaze in naturalistic and semi-naturalistic situations, reports in laboratory experiments are contradictory (Nation & Penny, 2008). These inconsistent results across studies could be due to methodological issues such as different age ranges, different task instructions or cues (static versus dynamic, schematic versus complex).

The majority of published reports find no evidence for deficits in attentional orienting to social stimuli in children and young individuals with ASD. For example, Swettenham et al. compared the performance of children with HFA (N=15, mean age=10.2 years) with 15 age- and IQ-matched controls on a cueing paradigm. The participants were instructed to detect a target appearing on the left or right of a centrally placed face cue. They observed that, despite instructions to ignore eye-movement in the face cue, both groups showed cueing effect and concluded that the attention shifts are reflexive (Swettenham, Condie, Campbell, Milne, & Coleman, 2003).

In another study by Kylliainen and Hietanen (2004), high-functioning children with autism (N=12, mean age=11.9 years, mean FSIQ=91) were compared with a group of tightly-matched controls. The cue was a photograph of a forward-facing head with the eyes statically gazing left or right. No group differences were detected in their study and both groups showed cueing effect (Kylliainen & Hietanen, 2004).

Some experiments have studied the effect of social cues such as eye gaze versus non-social cues (e.g. an arrow) in order to examine the sensitivity of social cues in ASD. It has been reported that individuals with ASD respond to social cues such as eye gaze in much the same way as they do to non-social cues such as arrows, whereas in non-autistic people, a greater salience to social cues has been reported (Chawarska, Klin, & Volkmar, 2003; Senju, et al., 2004).

Chawarska et al. studied toddlers with autism (N=15, mean age=2.23 years) who showed marked deficits in spontaneous gaze following during ADOS. They administered two experiments: in experiment 1, the cue was a photo of a face with moving eyes while in experiment 2, a non-biological movement (SimEyes) was used. The SimEyes was constructed to be similar to the eye-gaze cue. The cueing effect was observed for both ASD and control groups, suggesting that toddlers with ASD are sensitive to directional cues in eye movement although they do not seem to follow the gaze of others in naturalistic situations. They found that the controls were slower on eyes than SimEyes, whereas children with ASD showed equal RT across both experiments. Moreover, the infants with ASD were faster than controls in the eye-gaze cues (Chawarska, et al., 2003). Johnson replicated the latter finding, and speculated that faster RTs in infants with ASD may be a consequence of them not processing the central face as deeply as the typically developing infants do (Johnson et al., 2005).

Senju et al. compared the performance of a group of children with ASD (N=15 with mean age=10.11 years in experiment 1 and N=26 with mean age=9.6 years in experiment 2) to a group of age and IQ-matched controls using a cueing paradigm with a photo of a face as the social cue and an arrow as the non-social cue. In experiment 1, both groups showed the cueing effect in response to both uninformative gaze and arrow cues. Then, in experiment 2, they used counter informative arrow and gaze cues (the cue was predictive only in 20% of trials and counter-informative in 80% of trials) and observed that this time both eyes and arrows still yielded the cueing effect for children with ASD, whereas in controls, only the reflexive attentional orienting of the gaze cue survived this manipulation. They concluded that eye-gaze cues triggered reflexive orienting more effectively than arrow cues in control children, whereas the children with ASD did not show preferential sensitivity to a social cue (Senju, et al., 2004).

The finding of a lack of preferential sensitivity to social cues in infants and children with autism provide evidence for the idea that in ASD, social stimuli do not possess the normal pattern of increased salience, relative to non-social stimuli (Johnson, et al., 2005; Senju, et al., 2004).

It is suggested that whereas non-autistic individuals are alert to the social features of eye gaze stimuli, and respond via mechanisms developed to deal with social stimuli (Ristic, et al., 2002), individuals with ASD respond to physical features of the stimuli (e.g., motion) such that when these features are removed, reflexive attentional cueing via eye gaze is no longer observed (Ristic et al., 2005).

Ristic et al (2005) questioned the extent to which children with ASD are sensitive to eye gaze cues as social stimuli and assessed whether children with ASD show reflexive orienting of attention to eye gaze cues that are static and simple (comprising a left- or right-deviated gaze on a schematic face, rather than a photograph of a human face). They compared high-functioning autistic individuals (N=12) with a group of age and IQ-matched controls. They introduced two conditions: a) a non-predictive condition in which a target appeared at the gazed-at location 50% of the time and b) a predictive condition in which a target appeared at the gazed-at location 80% of the time. Both groups showed the cueing effect when eye direction was spatially predictive which indicates that they could perceive and use gaze direction as an attentional cue when the corresponding information was known to be helpful in performing the task. However, when the cue was non-predictive, only the control group shifted their attention in response to perceived eye direction, suggesting automatic but not voluntary orienting to gaze is impaired in ASD. The authors concluded that the controls but not the ASD group orient their attention automatically in response to gaze direction and are sensitive to eyes as displaying socially relevant information (Ristic, et al., 2005).

This finding by Ristic et al. is contradictory to the previous findings reporting that infants and children with ASD do show a normal cueing effect, even when the eye gaze cue is uninformative (Chawarska, et al., 2003; Kylliainen & Hietanen, 2004; Senju, et al., 2004; Swettenham, et al., 2003). The authors proposed that attentional orienting in previous work was underpinned by sensitivity to aspects of the stimulus such as motion, rather than sensitivity brought about by the special significance of social stimuli. For example, Swettenham et al. (2003) and Chawarska et al. (2003) used stimuli containing motion (i.e., eyes moving from a central fixation to look to the left or the right).

A recent study by Pruett et al. (2011) criticised the previous studies for not having included a full battery of control conditions, for not having varied cueing probabilities (except for Senju et al. (2004) and Ristic et al. (2005)), and for lacking rigorous control over eye position. They compared individuals with HFA (N=27, age range=9-12 years) to a group of age- and IQ-matched controls (N=25) on a Posner's paradigm variants. Participants were instructed to press a key as soon as they located a target and were asked to keep their eyes on the picture in the centre of the screen at all times. In their design, they assessed both exogenous orienting and endogenous orienting of attention using a different cue (i.e., a simple schematic box, face or

arrow) which preceded the target in each trial. They found that ASD children showed an almost identical pattern of results (across all conditions) compared to control children. They also found no evidence in support of ASD children responding more rapidly than controls for social versus non-social central attentional cues. The authors concluded that exogenous orienting, endogenous orienting, and gaze cueing appear to be intact in children with HFA and therefore, disrupted attentional redirection for shifts in others' gaze does not appear to be the explanation for gaze abnormalities and problems of social relatedness in ASD (Pruett et al., 2011).

In a standard Posner's paradigm, participants are cued to attend to a peripheral target without making eye movements and the above-mentioned studies assessed covert attention (except for Chawarska et al. (2003) and Johnson et al. (2005)).

Overt attention using a cueing paradigm which measures the saccadic reaction time (SRT) has been explored in control adults in some studies (Kuhn & Benson, 2007; Kuhn & Kingstone, 2009; Mansfield, Farroni, & Johnson, 2003). In these paradigms, participants are instructed to first fixate on a central fixation point; then the eye gaze of a centrally presented face shifts either to the right or the left and participants are asked to look at targets on either side of the screen as soon as possible. Participants are therefore required to saccade either in the same direction (congruent trials), or the opposite direction (incongruent trials) to which the eyes were pointing.

Cueing effect in healthy adults has been observed in overt orienting paradigm in response to both social and non-social cues even when the cue (gaze or arrow) was non-predictive (Kuhn & Benson, 2007) or counter-predictive (Kuhn & Kingstone, 2009) of the target location. Moreover, it has been shown that participants typically make more errors in incongruent than in congruent trials thus demonstrating that in healthy adults, gaze cues result in automatic gaze following (Kuhn & Benson, 2007; Kuhn & Kingstone, 2009). Mansfield et al. (2003) recorded eye movement latencies of healthy adults (N=12, mean age=24.8 years) to a target presented to the left or right of a face with averted gaze. Cueing effect was observed in this overt orienting paradigm. They reported that observing averted gaze could also elicit spontaneous saccades in the direction of the cue prior to target onset, even though participants were instructed to fixate on the centre during this period (Mansfield, et al., 2003).

There are a few studies which have explored overt attention using a cueing paradigm by measuring saccadic reaction time (SRT) in ASD (Kuhn et al., 2010). Such tasks offer a more direct way of investigating attentional abnormalities, as they are more closely related to the deviations in gaze following typically observed in ASD.

Kuhn et al. studied 12 high-functioning adults with ASD (mean age=26 years) in comparison to a group of age and IQ-matched controls (N=12, mean age=22.4 years). Their cueing paradigm was different from the classic ones because they used a changing colour dot as the cue and a schematic picture of a face or an arrow as distractor. Participants were instructed to move their

eyes to the right or left according to the colour of the solid dot. They were also explicitly told to ignore the distractors (see Figure 6-2).

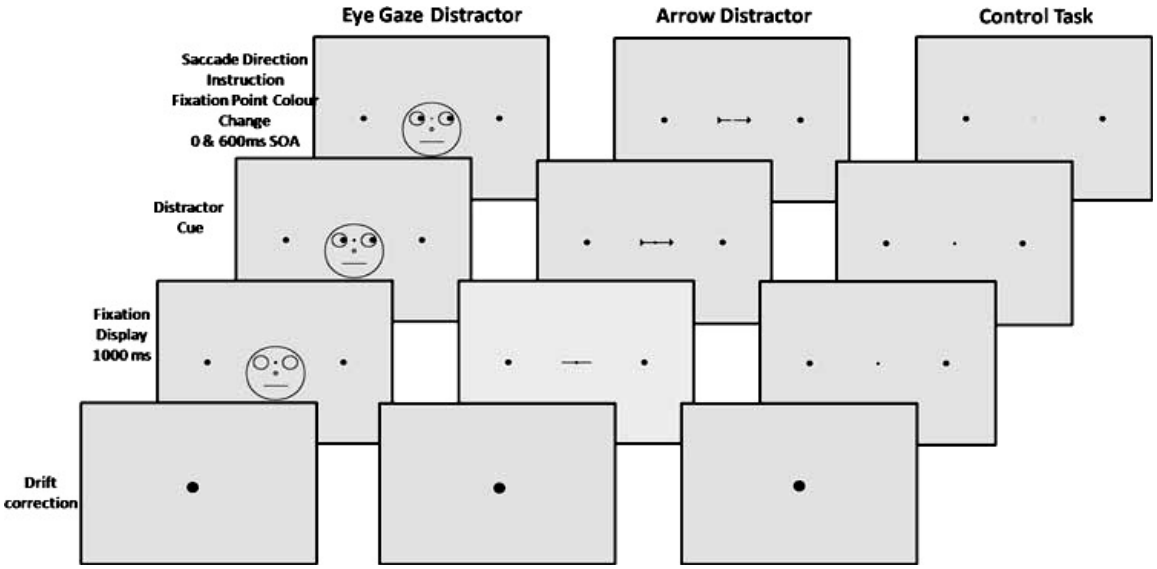


Figure 6-2: Sequence of events for each of the three conditions (Eye-gaze Distractor, Arrow Distractor, and Control Task)

(Figure from (Kuhn, et al., 2010))

They found that both groups responded in a similar way to both types of distractors (eye gaze and arrow) and similar cueing effects were found for both distractor types in both groups. Moreover, they observed that both groups responded significantly faster in the eye gaze trials, than in the arrow trials, which may reflect a general alerting effect by the eyes. They suggested that the lack of group difference might be due to the fact that individuals with HFA may learn some of the social skills which come naturally to controls, such as eye-gaze cueing and by the time they reach adulthood these differences are less apparent (Kuhn, et al., 2010).

6.7.4 Neural Correlates of Gaze Cueing and Orienting of Attention in ASD

The cortex along the superior temporal sulcus (STS) has been found to play a role in processing eye movements (Hoffman & Haxby, 2000). Anterior and superior displacements, as well as decreased bilateral grey matter volumes of the STS have been reported in young people with ASD (Boddaert, et al., 2004).

Plephrey et al., in two studies using the cueing paradigm, showed that whether the gaze of the centrally presented face was congruent or incongruent with a target location, a similar amount of STS activation was found in individuals with ASD, while normal controls showed more activation for the incongruent gaze condition (Pelphrey, Morris, & McCarthy, 2005; Pelphrey, Singerman, Allison, & McCarthy, 2003). This lack of STS modulation to a social context confirmed that, although a change in gaze direction was detected, its communicative and social value remained impaired in ASDs (Mosconi, Mack, McCarthy, & Pelphrey, 2005)

Senju et al.'s task investigated event-related potentials (ERP) in an explicit gaze direction discrimination task in which detection of specific eye direction was required of children with and without ASD. The detection of a change in eye direction elicited occipito-temporal negativity, which had two major differences between the groups: First, while this occipito-temporal negativity predominated in the right hemisphere of the control children, it was distributed equally bilaterally in children with ASD. Second, the amplitude of this negativity was more pronounced in control children in response to the detection of direct gaze as compared to averted gaze, but it was not sensitive to direct/averted gaze direction in children with ASD. The authors suggested that deviant neural substrates might be involved in gaze processing in individuals with ASD (Senju, et al., 2005).

As Itier and Batty concluded in their review, these data suggest an abnormal neural processing of gaze in ASD, which is linked to their abnormal perception of social cues and their impairments in ToM (Itier & Batty, 2009).

6.8 Summary

A ToM deficit is one of the prominent accounts trying to explain social and communication difficulties in autistic individuals. There are only a few studies that have compared ToM ability in children with diagnoses of ASD and ADHD in an attempt to identify whether ToM impairment is specific to ASD individuals. The findings from such studies are not consistent. Moreover, the studies showing ToM deficits in groups with ADHD have not taken into account the co-occurrence of the autistic symptoms in their sample. Therefore, it appears that there is a gap in the previous research on ToM which can be explored in the current study.

Another topic that has been extensively studied in ASD is the sensitivity of the individuals with ASD to social cues versus non-social cues. However, in most of these studies, the motor reaction time rather than SRT was recorded; there were only a few studies which explored overt attention using a cueing paradigm by directly measuring SRT in ASD (Kuhn, et al., 2010). Studying the SRTs offers a more direct way of investigating attentional abnormalities, as they are more closely related to the deviations in gaze following.

6.9 Aims & Hypotheses

This part of the study aims to replicate and extend previous findings from studies on childhood neurodevelopmental disorders in relation to the ToM account. It will help to determine: (1) whether the present sample confirms the ToM deficit account and social cognition abnormalities in the ASD group, (2) whether such impairments are specific to ASD and whether individuals with ASD can be distinguished from individuals with ADHD on the basis of their performance on the tasks assessing mentalising abilities and social cognition, (3) the impact of

comorbidity by comparing the performance of the comorbid group with the pure clinical groups and finally, (4) the effect of brain development on task performance will be evaluated.

6.10 Theory of Mind and Social Cognition Measures

Three established tests were used for the purpose of this study: the Triangle Task and the Strange Stories tapping ToM and a Social vs. Non-social Cueing task tapping social attention/cognition. These will be presented in three separate sections: Experiment 1, Experiment 2, and Experiment 3. At the end of the chapter, a summary of the key findings of each task with a conclusion will be presented.

6.10.1 Experiment 1: Triangle Task

The Triangle Task was based on that used in Abell& Happé (2000). They devised a set of animations involving two triangles, the movement of which could be described in terms of a goal-directed action or could evoke mental state attributions (Abell, et al., 2000).

6.10.1.1 Method

The test involves a series of computer-presented animations presented to participants in succession. The animations showed one large red and one small blue triangle moving around the screen on a white background, which in most trials were contained within an enclosure. The protagonists were the two triangles. This restricted cues for mental state attributions to pure movement and interaction without vocal or facial expression cues.

Five animations were used for the purpose of this study in two conditions: one goal-directed animation (G-D), and four ToM animations. In the G-D condition, one triangle was responding to the other triangle's behaviour, and was likely to evoke direct descriptions of interaction. The animation selected for this study was *'Leading'* in which the smaller triangle was following the bigger one. Although participants could still attribute mental state to this animation, it was not designed to evoke such descriptions.

In the ToM animations, by contrast, one character was portrayed as reacting to the other character's mental state. They were designed by the creator to produce mental state attributions, although they may not. The themes were a) *Coaxing* in which the big triangle tries to coax the small one out of an enclosure; b) *Surprising* in which the small one played tricks and hid behind a door to surprise the big triangle; c) *Mocking* in which the small triangle mocked the big one behind its back; and d) *Seducing* in which one character tried to seduce and persuade the other to let it go free. In all the animations, the triangles moved as if self-propelled. The animations were approximately matched in length, all lasting between 34 and 45 sec. An example of a ToM animation (the coaxing sequence) is shown by means of five stills in Figure 6-3.

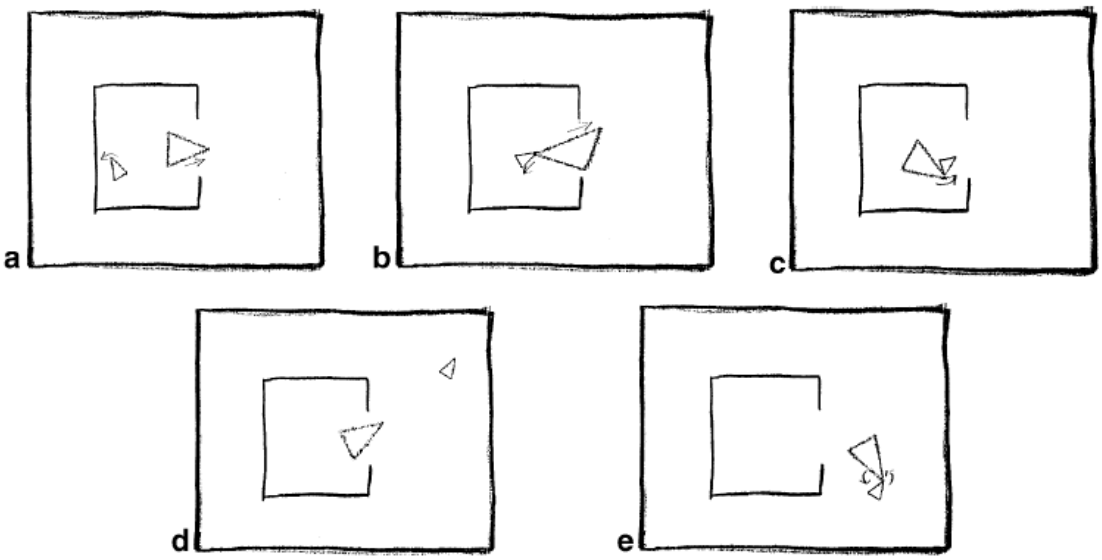


Figure 6-3: Five Stills from 'Coaxing' Animation.

(Figure from (Abell, et al., 2000)). An example of description: (a) Mother tries to interest child in going outside. (b) Child is reluctant to go out. (c) Mother gently nudges child towards door. (d) Child explores outside. (e) Mother and child play happily.

6.10.1.2 Procedure

Animations were presented on a computer in a fixed order: first the G-D animation and then ToM conditions were presented (a to d) and participants were asked to describe what they thought the two triangles were doing. Participants' responses were written down by the experimenter and also audiotaped for a detailed transcription and scoring. No feedback was given, except general encouragement.

6.10.1.3 Scoring

The scores of appropriateness and intentionality were assigned to each description separately following Castelli et al.'s study (Castelli, et al., 2000). The two performance variables were the appropriateness score, reflecting how accurate the description was to the intended scripts, and the intentionality score, reflecting the ability of participants to attribute mental states to the animations.

Responses were assigned an appropriateness score (range 0-3) according to their level of accuracy: Score 0, if the participant did not give any response; score 1, if the description of an action was not related to the events or was relates to a very minor aspect of the sequence only; score of 2, if the description was partially correct; and score 3, if the description was correct.

Each response was also assigned an intentionality score (range 0-5), independent of the appropriateness score, as follows: score 0, for non deliberate actions, i.e. a simple action

statement with no explicit mention of interaction between the triangles, or mental state/psychological language (e.g. Bouncing); score 1, for deliberate actions with no involvement of others (e.g. Ice-skating, Swimming); score 2, for deliberate actions with somebody else, i.e. any response that explicitly mentions interaction between the triangles, without reference to mental state/psychological language (e.g. Leading, Hugging); score 3, for deliberate action in response to other's action (e.g. Pushing back, Chasing); score 4, for deliberate actions with reference to mental states (e.g. Want, Encouragement); and finally score 5, for deliberate action with explicit mention of a goal of affecting other's mental state (e.g. Surprising, Bullying).

Appropriateness and intentionality scores were somewhat independent. Thus, an individual might score high for intentionality even if their answer was of a type not expected for the particular animation condition. Detailed scoring criteria are shown in Appendix D.

Two raters scored all the animations. Overall agreement was high (95%, kappa=.79), and disagreements were resolved between the two raters during a consensus meeting.

6.10.1.4 Hypotheses

Given the impairments in mentalising abilities as evident in ASD, it was expected that children and adolescents with ASD would be more impaired in the attribution of social intention to abstract stimulus material. Therefore, it was expected that individuals with ASD would show lower appropriateness and intentionality scores compared to the control group. It was also predicted that a strong association would be present between the Triangle Task performance and clinical measures of ASD behaviour, specifically in measures of social and communication skills.

Based on the studies that reported impairment in ToM abilities and social perception in the ADHD group, it was also predicted that difficulties would be observed in this group compared to controls in attributing mental states to triangles. However, no a priori hypothesis was considered as to whether the ToM ability was more impaired in the ADHD or ASD individual.

On a more exploratory ground, it was predicted that poorer performance would be seen in the comorbid group than the controls in the Triangle Task. However, no assumption was made regarding the level of impairment.

6.10.1.5 Results from the Triangle Task

Data were available from 110 individuals including 18 ASD, 34 ADHD, 38 comorbid, and 20 controls. Table 6-1 presents demographic information by group for participants who completed the Triangle Task.

No significant differences in age among the groups ($p>.05$) were observed. However, significant differences were found for FSIQ, PIQ, and VIQ (all $p<.05$). Further analysis showed that the

two groups of children with ADHD symptomatology (pure ADHD and comorbid groups) had significantly lower FSIQ, PIQ, and VIQ compared to controls (LSD post-hoc tests, all $p<.05$), whereas the ASD group did not differ from controls ($p>.05$ for FSIQ, PIQ, and VIQ comparisons).

The ASD group had a significantly higher FSIQ relative to the ADHD group ($p<.05$), but not the comorbid group ($p>.05$). No differences amongst the three clinical groups were observed in PIQ and VIQ (all $p>.05$).

Table 6-1: Group descriptive for participants who completed the Triangle Task: Means (SD), [Range]

	ASD (N=18)	**ADHD (N=34)**	**Comorbid (N=38)**	**Controls (N=20)**	**$F_{(3,106)}$**	**P**	**Post-hoc LSD**
Age in month	135.06(18.90)	132.97(32.08)	128.33(26.38)	125.10(29.59)	.57	.63	
[Range]	[96-168]	[84-191]	[87-200]	[91-180]			
FSIQ	112.17(16.15)	100.88(14.32)	106.13(13.05)	121.60(13.66)	9.83	<.001	Controls> ADHD, Comorbid*
[Range]	[77-139]	[70-135]	[82-142]	[102-149]			ASD>ADHD*
PIQ	108.50(14.83)	99.18(14.01)	105.21(12.82)	115.25(12.78)	6.23	.001	Controls> ADHD, Comorbid*
[Range]	[80-136]	[64-131]	[77-141]	[100-141]			
VIQ	113.33(18.61)	102.53(16.09)	105.58(14.53)	123.00(14.67)	8.22	<.001	Controls> ADHD, Comorbid*
[Range]	[78-145]	[75-133]	[77-146]	[99-151]			

**Post-hoc test, p<.05*

6.10.1.5.1 Group Comparisons on the Triangle Task

There was only one animation for the physical condition (G-D animation), whereas four different animations were used for the mentalising condition (ToM animations). To make the comparison between the animations clearer, the mean scores of the four ToM animations were calculated for intentionality and appropriateness.

Initially, analyses were conducted without adjusting for age and IQ. Group differences were explored using ANOVA with group as the between-subjects factor. Figure 6-4 depicts the mean scores in intentionality and appropriateness for each group. Table 6-2 shows descriptive statistics (mean, standard deviation) for the Triangle Task.

It can be seen that all groups seemed to be performing at the same level on the physical G-D animation both in terms of intentionality ($F_{(3,106)}$=.71, p=.55, η^2=0.020) and appropriateness ($F_{(3,106)}$=.19, p=.90, η^2=0.005). Moreover, no group differences were found in terms of intentionality ($F_{(3,106)}$=.28, p=.84, η^2=0.008) and appropriateness ($F_{(3,106)}$=.79, p=.50, η^2=0.022) in ToM animations.

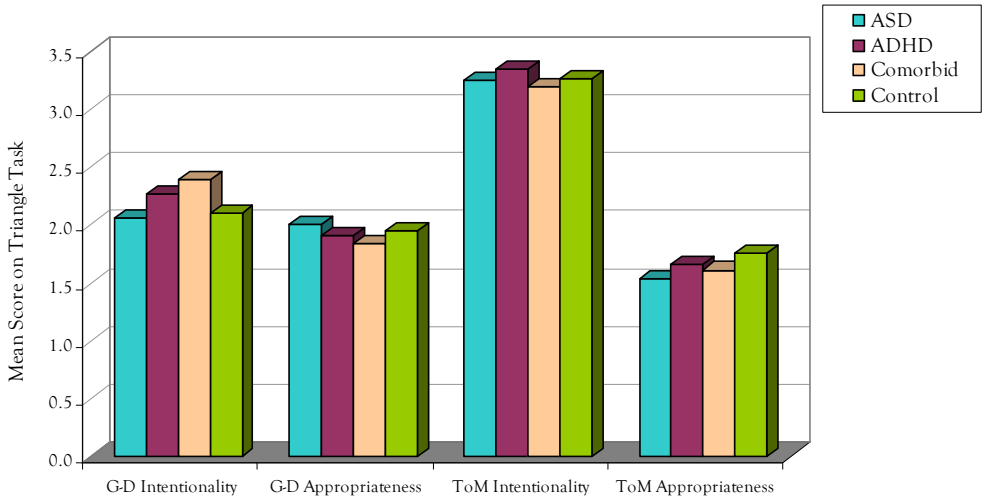


Figure 6-4: Mean Intentionality and Appropriateness Score by group

The effect sizes were calculated for pairwise comparisons (Table 6-3). There was a medium effect size for the comparisons between the ASD group and controls (d=.49) and also between the comorbid group and controls (d=.33) for the ToM appropriateness score, with controls being more accurate than the two groups with ASD. It is important to mention that the power of these analyses were limited for a .05 two-sided level of significance (power=.32 and power=.22; respectively).

Differences in the task condition were further explored using a repeated measure ANOVA with group as the between-subjects factor and task condition (Physical/Mentalising) as the within-subjects factor. For the intentionality score, there was a significant main effect of condition

($F_{(1,106)}$=97.06, p<.001, η^2=0.478), indicating that the ToM intentionality score was higher than the G-D intentionality score. The group by condition interaction was not significant ($F_{(3,106)}$=.84, p=.48, η^2=0.023), which indicates that the intentionality scores were higher for the ToM than G-D condition in all groups.

A significant main effect of condition was also observed for the appropriateness score ($F_{(1,106)}$=10.75, p=.001, η^2=0.092) with the G-D appropriateness score higher than the ToM appropriateness score. The group by condition interaction was not significant ($F_{(3,106)}$=.39, p=.8, η^2=0.011), which suggests that the appropriateness scores were higher for the G-D than the ToM condition for all groups.

In order to test the hypothesis that individuals with ASD would show poorer performance on the Triangle Task, the two groups with ASD (i.e. pure ASD and comorbid groups) were combined into one group with ASD (N=56) and the ADHD and control groups were collapsed into a non-ASD group (N=54) (Figure 6-5). The two groups were matched on age ($t_{(108)}$=.08, p=.93) and FSIQ ($t_{(108)}$=.16, p=.87).

Independent sample t-tests showed no significant differences between the two groups in Triangle Task measures on goal-directed animations: G-D intentionality ($t_{(108)}$=.45, p=.65, d=.09) and G-D appropriateness ($t_{(108)}$=.22, p=.82, d=-.05). Moreover, for the ToM animations, even though the group with ASD had a lower score on both intentionality and appropriateness, the group differences did not reach significance: ToM intentionality ($t_{(108)}$=.76, p=.45, d=-.15) and ToM appropriateness ($t_{(108)}$=1.25, p=.21, d=-.24).

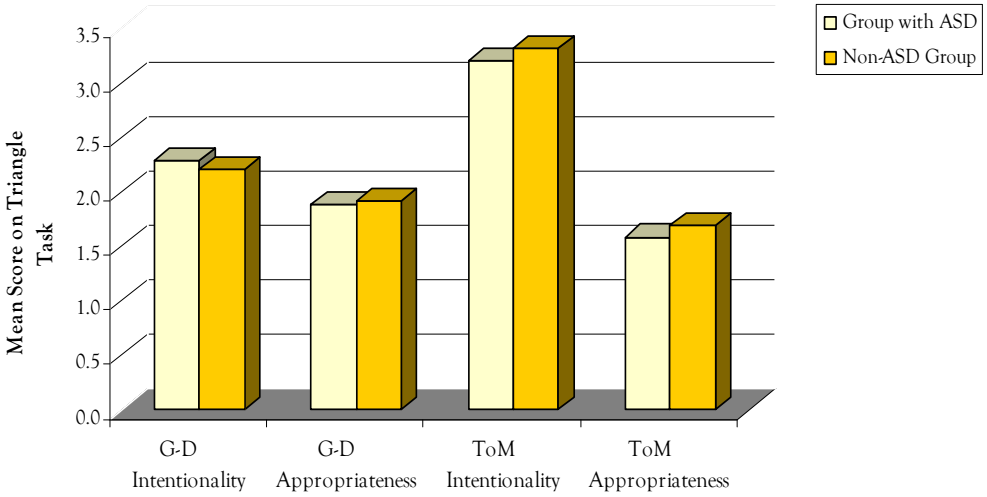


Figure 6-5: Mean Intentionality and Appropriateness Score in group with ASD vs. non-ASD group

All the above analyses were repeated adjusting for age and IQ. As the Triangle Task was verbally demanding, the effect of VIQ was evaluated instead of FSIQ. ANCOVA was run on the task variables with group as the between-subjects variable and age and VIQ as covariates.

When adjusted for age and VIQ, separately, the findings did not substantially differ from the analysis unadjusted. In addition, age and VIQ were entered as covariates together. Again no differences were observed from the analysis unadjusted (As the findings did not change after controlling for age and VIQ, in order not to be repetitive the statistics were not reported).

Table 6-2: Group comparisons on Triangle Task: Means (SD)

	ASD (N=18)	ADHD (N=34)	Comorbid (N=38)	Control (N=20)	Group effect	
					$F_{(3,106)}$	P
G-D Intentionality Score (range 0-5)	2.06(.64)	2.26(.83)	2.39(1.13)	2.10(1.02)	.71	.55
G-D Appropriateness Score (range 0-3)	2.00(.84)	1.91(.75)	1.84(.75)	1.95(.83)	.19	.90
ToM Intentionality Score (range 0-5)	3.25(.59)	3.35(.74)	3.20(.74)	3.26(.74)	.28	.84
ToM Appropriateness Score (range 0-3)	1.54(.44)	1.66(.51)	1.61(.45)	1.76(.46)	.79	.50

Table 6-3: Effect sizes (d) of the Triangle Task

	Control-ASD	Control-ADHD	Control-Comorbid	ASD-ADHD	ASD-Comorbid	Comorbid-ADHD
G-D Intentionality Score	.05	-17	-.29	-.27	-.36	-.13
G-D Appropriateness Score	-.06	.05	.14	.11	.20	-.09
ToM Intentionality Score	.01	-.12	.08	-.15	.07	-.20
ToM Appropriateness Score	.49	.20	.33	-.25	-.16	-10

6.10.1.5.2 Effects of Age and IQ

Table 6-4 shows the correlation between the Triangle Task variables; age, FSIQ, and VIQ across all groups. Overall, age was significantly correlated with all task measures except for the G-D intentionality score, whereas VIQ was not significantly correlated with any performance variables (*r* values are given in the table).

Correlation analyses were then performed for each group separately (see Table 6-5). In the control group, there was a significant correlation between ToM appropriateness and age (r=.50, p=.01) with older children providing more correct descriptions.

In the ASD group, a significant correlation was observed for G-D appropriateness and age (r=.44, p=.03). In addition, VIQ was significantly correlated with G-D intentionality (r=.44, p=.03) and G-D appropriateness (r=.44, p=.03) scores indicating that the higher the VIQ, the better the performance on the G-D animation description.

In the ADHD group, age was significantly correlated with ToM intentionality (r=.54, p<.001) and ToM appropriateness (r=.35, p=.02), with scores indicating better performance on ToM animations in older participants.

Finally, in the comorbid group, age was significantly correlated with all of the Triangle Task variables: G-D intentionality (r=.29, p=.04), G-D appropriateness (r=.41, p=.005), ToM intentionality (r=.38, p=.009) and ToM appropriateness (r=.40, p=.006) scores.

In order to compare the magnitude of correlations between group, Fisher's r-to-z transformation was carried out which showed no significant differences (all p>.05), indicating that the effect of age and VIQ on the task performance was similar in different groups.

Table 6-4: Correlation between Triangle Task measures, age and VIQ across all groups

	G-D Intentionality Score	G-D Appropriateness Score	ToM Intentionality Score	ToM Appropriateness Score
Age	.12	.24**	.40**	.36**
VIQ	-.02	.12	.001	.02

*** Correlation is significant at the 0.01 level.*

Table 6-5: Correlation between Triangle Task measures, age and VIQ for each group

	G-D Intentionality Score		G-D Appropriateness Score		ToM Intentionality Score		ToM Appropriateness Score	
	Age	**VIQ**	**Age**	**VIQ**	**Age**	**VIQ**	**Age**	**VIQ**
ASD	.11	.44*	.44*	.44*	.07	.05	.22	.01
ADHD	-.08	.11	.13	.11	.54**	.003	.35*	.12
Comorbid	.29*	-.07	.41**	-.004	.38**	-.11	.40**	-.11
Control	.13	-.17	.08	-.02	.34	.22	.50*	-.10

** Correlation is significant at the 0.05 level,* *** Correlation is significant at the 0.01 level*

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6.10.1.5.3 Correlations between Task Measures and Clinical Measures

Correlations between Triangle Task measures and clinical measures including Conners score, SCQ and selective scores of SDQ (SDQ total score and SDQ hyperactivity) were assessed across the groups (see Table 6-6).

Table 6-6: Correlation between Triangle Task measures and clinical measures across all groups

	Conners Inattention	Conners Hyperactivity /Impulsivity	SCQ	SDQ Total	SDQ Hyperactivity
G-D Intentionality	.01	.09	.04	.06	-.02
G-D Appropriateness	-.11	-.05	.01	-.07	-.08
ToM Intentionality	.05	.07	-.07	-.16	-.19*
ToM Appropriateness	-.03	.03	-.09	-.10	-.06

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level*

In order to address whether performance on the Triangle Task was related to clinical measures of ASD and ADHD behaviours, further analyses were carried out with the clinical data within each group (see Table 6-7). No significant correlation was observed in the control group.

In the ADHD group, there was a significant correlation between PACS inattention and G-D appropriateness (r=-.40, p=.009), indicating less accurate responses in those with higher inattention scores. There was also a significant correlation between PACS hyperactivity and ToM intentionality (r=-.29, p=.04), suggesting a less frequent tendency to attribute mental states in those with more hyperactive symptoms. All correlations remained significant after controlling for the effects of age and FSIQ, separately.

In the combined group with ASD, there was a significant correlation between the ADOS communication score and ToM appropriateness (r=-.31, p=.02), indicating that a greater difficulty with communication would lead to less accurate responses in ToM animations. The correlation remained significant after controlling for the effects of age and FSIQ, separately.

No significant correlations were observed in the pure ASD group between the task measures and clinical measures.

Finally, in the comorbid group, the Triangle Task performance was related to autistic behaviours. A significant correlation was observed between the ADOS communication score and G-D intentionality (r=-.29, p=.04) and ToM appropriateness (r=-.45, p=.003) scores. Moreover, the RRIB score, as measured by the ADOS and ADI-R was associated with ToM

appropriateness (r=-.30, p=.04 for ADOS RRIB, and r=-.28, p=.04 for ADI-R RRIB). All correlations remained significant after controlling for the effects of age and FSIQ, separately.

Table 6-7: Correlation between Triangle Task measures and clinical measures for each group (Unadjusted for age and VIQ)

	G-D Intentionality Score	G-D Appropriateness Score	ToM Intentionality Score	ToM Appropriateness Score
Controls				
Conners Inattention	.32	.33	-.16	-.20
Conners Hyperactivity /Impulsivity	.06	-.01	-.16	-.24
SCQ	-.33	.26	-.09	-.07
SDQ Total	-.12	-.23	-.12	-.39
SDQ Hyperactivity	.18	-.26	-.41	-.40
ASD				
Conners Inattention	-.20	-.33	.01	.05
Conners Hyperactivity /Impulsivity	-.15	-.19	-.14	-.21
SCQ	-.06	-.02	-.24	.01
SDQ Total	.28	.11	.10	.32
SDQ Hyperactivity	.28	.24	-.24	.30
ADHD				
Conners Inattention	-.08	-.20	.16	.008
Conners Hyperactivity /Impulsivity	-.27	-.26	.28	.17
SCQ	.17	-.14	-.008	-.07
SDQ Total	.26	-.07	.03	.10
SDQ Hyperactivity	-.28	-.11	-.003	-.04
Comorbid				
Conners Inattention	-.13	.07	.18	.11
Conners Hyperactivity /Impulsivity	.16	.25	.25	.25
SCQ	-.03	.17	.02	.03
SDQ Total	-.37*	-.002	-.23	-.22
SDQ Hyperactivity	-.12	.14	-.23	-.02

**Correlation is significant at the 0.05 level,* ***Correlation is significant at the 0.01 level*

6.10.1.6 Discussion of the Triangle Tasks

The Triangle Task has been used previously to assess the ability of individuals with ASD to attribute mental states to geometric figures in different contexts (Abell, et al., 2000). This is the first study comparing the performance of individuals with ASD to individuals with ADHD and a comorbid group in the Triangle Task.

In the present sample, no group differences were found in the Triangle Task. All groups performed at the same level in both goal-directed and mentalising animations in terms of intentionality (i.e. attributing mental states to triangles) and appropriateness (i.e. understanding the intended meaning of the animation sequences).

ASD individuals in the current sample were able to attribute mental states to triangles at the level of the control group. This finding is in line with the study done by Salter et al. (Salter, et al., 2008). However, it is in contrast to Castelli's findings which reported fewer mental state descriptions in their group of adults with Asperger's disorder matched for verbal and non-verbal ability to a control group (Castelli, et al., 2002).

Individuals with ASD could also accurately describe animations that were designed to evoke ToM- related descriptions. This finding does not support previous studies which found less appropriate mental state descriptions in the ASD group as compared with controls for ToM animations (Abell, et al., 2000; Castelli, et al., 2002; Salter, et al., 2008).

The finding of ToM competence in the ASD group compared with the control group is in line with the studies that suggest normal intellectual, in particular, verbal abilities scaffold ToM abilities and that therefore, individuals with HFA show ToM competencies, at least in structured and verbally mediated situations (Bowler, 1992).

The difference between the present findings and those reported by Abell et al. (Abell, et al., 2000) might be due to different methodology both in terms of participants' abilities and task instructions. In their study, the participants were matched on verbal mental age but had low verbal ability compared to controls. Their ASD group had a VIQ of 75, and their control group had a VIQ of 102; whereas in the current study, all the groups were more able in terms of verbal ability and FSIQ. Moreover, in Abell's study, in the G-D condition, the triangles were given animal roles by the experimenter (for example, mother duck and duckling) and in the ToM animations the triangles were identified as people (for example, grandma and grandson). This might have cued participants to look for social interaction between the characters; however, it might have prompted the individuals in the ASD and control groups differently.

The two groups with ADHD performed similarly to the ASD group and the Triangle Task could not distinguish between the clinical groups. The ToM competence in the ADHD group is

in contrast to the studies reporting a ToM deficit in individuals with ADHD (Buitelaar, Van der Gaag, Klin, & Volkmar, 1999; Fine, et al., 2008).

Developmental improvement in the Triangle Task was evident in all groups and was relatively the same in the clinical and control groups. Moreover, it seems that mentalising was independent of cognitive and verbal ability in all groups in the present sample.

Autistic behaviours, in particular communication difficulties and restricted, repetitive interests and behaviours, were related to less accurate descriptions in animations with mental state contents: this reflects the difficulties children with autistic symptomatology have in understanding social situations. However, as discussed in the current study, the two groups with ASD (i.e. the pure ASD group and comorbid group) were able to perform the task at the level of age-matched controls which may be due to compensatory mechanisms such as high cognitive and verbal ability in these groups.

It appeared that the performance of individuals in the ADHD group was to some extent negatively affected by their inattention and hyperactivity/impulsivity symptoms; however, in this set of short cartoons, individuals with ADHD could perform the task at the level of age-matched controls.

This study did not support the initial hypothesis that the use of animated cartoons to measure ToM skills would provide better discrimination between verbally able autistic and non-autistic children. It might be the case that the Triangle Task is a relatively easy task for autistic individuals with high cognitive and verbal abilities and a more complex task similar to naturalistic social situations is needed to challenge their ToM ability.

Another explanation for the lack of findings in the current study could be the method of scoring the Triangle Task. This has been previously mentioned by Salter et al. (2008) who argued that the scoring system is limited by the fact that the appropriateness scores are restricted to a 0–2 scale, and intentionality scores to a 0–5 scale. Moreover, the frequency of the use of mentalising language is not taken into account by the current scoring procedure (Salter, et al., 2008). Given all the above reasons, the current scoring system might not be sensitive enough to capture all of the elements of the transcripts that distinguish the groups.

Salter et al. further analysed their transcripts and reported that, despite no group differences being observed in terms of the intentionality score, there was a clear difference between the groups in the appropriate use of mentalising language to accurately describe the ToM animations (Salter, et al., 2008).

It also has been suggested by Klin (2000) that the transcripts may be a more informative way to demonstrate subtle differences between adults with ASD and controls. He observed that the ASD individuals used considerably fewer relevant mental state terms in the Social Attribution

Task he administered. Qualitative analysis of the transcripts further revealed that some individuals within the ASD group frequently used mental state terms in their descriptions, but that they were not appropriately related to the animations (Klin, 2000).

6.10.1.7 Conclusion

The current study extends previous research by comparing the ASD group to a group of age and IQ-matched controls. It is the first to compare the performance of ASD individuals with ADHD individuals in the Triangle Task and to take into account the co-occurrence of the symptoms of ASD and ADHD when comparing the two groups.

All groups performed at the same level on both goal-directed and mentalising tasks in terms of intentionality (i.e. attributing mental states to triangles) and appropriateness (i.e. understanding the intended meaning of the animation sequences) and the task could not discriminate between the groups.

The finding of ToM competence in the ASD group compared with the control group suggests that the Triangle Task may be a relatively easy task for ASD individuals with high cognitive and verbal ability and a more complex task similar to naturalistic social situations is needed to challenge their ToM ability.

6.10.1.8 Limitations and Suggestions for Future Research

The present study was undertaken in children and adolescents with HFA and Asperger's disorder with high verbal abilities. Therefore, the results deriving from this study cannot be generalised to ASD populations with below average verbal abilities.

Further limitations included the sample size, which was relatively small and unequal, although comparable to previous studies; the participants' age range was quite wide; and, the number of animations used was relatively low (only one animation in the G-D condition and four animations in the ToM condition).

It is suggested that future research reassess the Triangle Task performance of individuals with ASD in comparison to alternative control groups such as an ADHD group, using a larger sample and more animations in both contexts. It is also recommended that the co-occurrence of ADHD in an ASD group is considered in order to control for its confounding effect.

It is also suggested that the descriptions provided by the participants be further examined qualitatively as well as quantitatively. This would possibly help to capture the elements that distinguish individuals' performance.

6.10.2 Experiment 2: Strange Stories

This task is a test of advanced ToM, first introduced by Happé (Happe, 1994a), which is suitable for both higher functioning children and adults. Happé's (1994) original set included 24

stories accompanied by a smaller set of six control stories. All participants in Happé's study performed at ceiling on the control stories, which were not matched for difficulty with the mental state stories. Later, Fletcher et al. (1995) modified the control stories by creating new physical stories which were matched to the mental state set in terms of difficulty.

6.10.2.1 Method

A set of 10 stories, including five stories with mental state content, selected from the original Strange Stories test (Happe, 1994a) and five control stories with physical content, selected from the set of stories created by Fletcher et al. (1995) (Fletcher, et al., 1995) were chosen (see Appendix D). Control stories were given to check the generality of any comprehension deficits which might emerge regardless of story content.

For the mentalising stories, correct performance involved accurately identifying accurately the underlying intention behind a character's utterance that was not literally true. The stories used assessed the ability to understand lies, white lies, double bluff, persuasion and misunderstanding. For the physical stories, participants were expected to identify a physical or practical reason for the character's words or actions.

6.10.2.2 Procedure

For the ease of administering the test, the vignettes were recorded and then presented to the participants one after the other. The participants were instructed to listen carefully to the story and to answer the questions which followed. First, a practice story was given to familiarise participants with the task's requirements.

All five vignettes of one condition were given together, but the order of the 2 conditions was counterbalanced (participant 1 gets Mental state then Physical stories; participant 2 gets Physical then Mental state stories).

The participants' responses were written down by the experimenter and audiotaped for detailed scoring.

6.10.2.3 Scoring

The stories were rated in terms of accuracy on a 0–2 scale as follows: score 0, for an incorrect answer; score 1, for incomplete or partially correct answer; and score 2, for a fully correct and complete answer (see Appendix E for scoring criteria and examples).

For example, in the mentalising story involving double bluffing, called the 'brothers', a 2-point answer might be: *Simon tried to trick his brother but Jim knew Simon would lie so he looked in the cupboard.* A 1- point answer for the same story would demonstrate partial understanding such as: *He went to the cupboard because that's where his ping-pong paddle was.* A 0-point answer would be incorrect, such as: *Paddles are usually kept in cupboards.*

In the physical story involving a burglar alarm being set off during a burglary, a 2-point answer might be: *The burglar disturbed the cat which set the alarm off*. A 1-point answer for the same story would demonstrate partial understanding such as: T*he burglar was disturbed by the cat and set the alarm off*. A 0-point answer would be incorrect, such as: *The animal's scream set the alarm off*.

Two raters scored all the stories. Overall agreement was relatively high (95%, kappa=.73), and disagreements were resolved between the two raters during a consensus meeting.

6.10.2.4 Hypotheses

Given the impairments in mentalising ability as previously suggested in ASD, it was predicted that individuals with ASD would have greater difficulty in understanding of the social stories than the controls. It was also expected that a strong association would be present between the Strange Stories task performance and clinical measures of ASD behaviour, specifically measures of social and communication skills.

There is one study that has assessed the Strange Stories task in ADHD (Charman, et al., 2001), which found no differences between the ADHD and control groups in their performance. However, given the generalised attentional problems in ADHD, it was predicted that poor performance would be seen across all stories, independent of the stories' content. It was furthermore predicted that while individuals with ASD would show specific impairment in stories with social content, individuals with ADHD would show difficulties in both social and physical stories.

No study has explored the Strange Stories task performance in individuals with a diagnosis of comorbid ASD and ADHD. Therefore, on a more exploratory ground, it was predicted that poorer performance would be seen in the comorbid group than in the control group. However, no assumption was made regarding the level of impairment and whether the pattern of performance would be more similar to the ASD or ADHD groups.

6.10.2.5 Results from Strange Stories Task

As Strange Stories was introduced later during the study, data were available from only 82 individuals including 13 ASD, 20ADHD, 30 comorbid, and 19 controls.

Table 6-8 presents demographic information by group for participants who completed the Strange Stories task.

No significant differences in age among the groups (p>.05) were observed. However, significant differences were found for FSIQ, PIQ, and VIQ (all p<.05). Further analysis showed that the two groups of children with ADHD symptomatology (pure ADHD and comorbid groups) had significantly lower FSIQ, PIQ, and VIQ compared to controls (LSD post-hoc tests, all p<.05),

whereas the ASD group did not differ from controls (all p>.05). No significant differences amongst the clinical groups were observed for FSIQ, PIQ, and VIQ (all p>.05).

Table 6-8: Group descriptive for participants who completed the Strange Stories Task: Means (SD), [Range]

	ASD (N=13)	ADHD (N=20)	Comorbid (N=30)	Controls (N=19)	$F_{(3,78)}$	P	Post-hoc LSD
Age in month	131.38(18.47)	134.15(32.19)	131.68 (26.42)	126.63(29.58)	.25	.86	
[Range]	[96-168]	[86-191]	[94-200]	[91-180]			
FSIQ	111.92(18.91)	101.30(13.31)	105.00 (12.22)	122.63(13.20)	9.11	<.001	Controls> ADHD, Comorbid*
[Range]	[77-139]	[75-135]	[79-129]	[104-149]			
PIQ	107.85(16.89)	100.65(14.18)	103.47(13.31)	115.79(12.89)	4.43	.006	Controls> ADHD, Comorbid*
[Range]	[80-136]	[64-131]	[75-141]	[100-141]			
VIQ	113.46(19.89)	101.55(13.66)	105.30(13.70)	124.26(13.91)	9.23	<.001	Controls> ADHD, Comorbid*
[Range]	[78-145]	[82-131]	[77-137]	[102-151]			

**Post-hoc test, p<.05,*

6.10.2.5.1 Group Comparisons in the Strange Stories Task

Initial analyses were conducted without adjusting for age and IQ. Group differences were explored using ANOVA with group as the between-subjects factor.

Figure 6-6 depicts the mean scores on mental state and physical stories, separately for each group and Table 6-9 shows descriptive statistics (mean, standard deviation) in the Strange Stories task.

It can be seen that all groups seemed to be performing at the same level for physical stories ($F_{(3,78)}$=.33, p=.81, η^2=0.013) showing that the clinical groups were able to comprehend the control stories at the level of the control group.

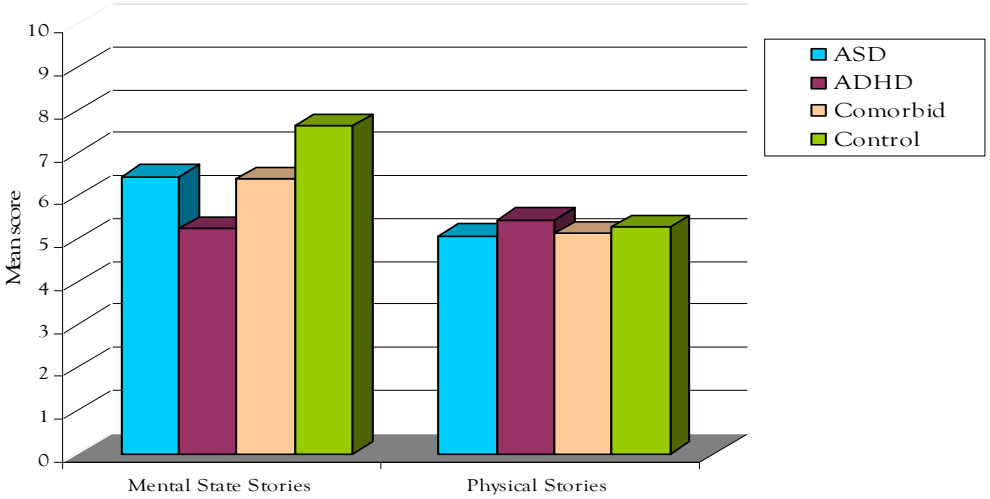


Figure 6-6: Mean Score on Strange Stories Task (Mental State vs. Physical) by group

Significant group differences were found in the mental state stories ($F_{(3,78)}$=2.99, p=.04, η^2=0.103). The control group performed better than the three clinical groups in mental state stories; however, the difference was only significant between ADHD and controls (p=.004) and the difference between ASD and controls (p=.19) and comorbid and control groups (p=.09) did not reach significance. Moreover, no significant differences were observed between clinical groups (all p>.05).

The effect sizes were calculated for pairwise comparisons (see Table 6-10). As is shown there was a medium effect size for the comparisons between the ASD group and controls (d=.45) and also between the comorbid group and controls (d=.52) for mental state stories. The power of these analyses was limited for a .05 two-sided level of significance (power=.23 for ASD and control comparison, and power=.43 for comorbid and control comparison). Moreover, a medium effect size was observed for the comparisons between the ASD and ADHD groups (d=.45) and also between the comorbid and ADHD groups (d=.47) for mental state stories.

However, the power of these analyses was limited for a .05 two-sided level of significance (power=.24 for ASD and ADHD comparison, and power=.36 for comorbid and ADHD comparison).

All the above analyses were repeated, adjusting for age and IQ. As the Strange Stories task was verbally demanding, the effect of VIQ was evaluated instead of FSIQ. ANCOVA was run on the task variables with group as the between-subjects variable and age and VIQ as covariates. When adjusted for age and then separately for VIQ, and finally for both age and VIQ, the findings on physical stories did not differ from the analysis unadjusted (as the findings did not change, in order not to be repetitive the statistics were not reported).

Significant group differences in mental state stories score were still observed after controlling for age ($F_{(3,77)}$=3.83, p=.01, η^2=0.130), with the post-hoc tests showing a significantly better score in controls than in ADHD (p=.001) and comorbid groups (p=.05); however, when adjusted for VIQ, the group differences in mental state stories disappeared ($F_{(3,77)}$=.74, p=.53, η^2=0.028). Furthermore, both age and VIQ were entered as covariates. The findings were similar to the time only VIQ was entered (as the findings did not change after controlling for age and VIQ, in order not to be repetitive, the statistics were not reported).

Repeated measure ANOVA was carried out with group as the between-subjects factor and the story content (mental state versus physical) as the within-subjects factor. No significant group differences were found ($F_{(3,78)}$=1.47, p=.23, η^2=0.054). There was a significant main effect of story content ($F_{(1,78)}$=13.73, p<.001, η^2=0.150), reflecting the lower score on physical stories compared to mental state stories, suggesting that the physical stories were generally more difficult compared to mental state stories in the present sample. Group by story content interaction showed a trend towards significance ($F_{(3,78)}$=1.24, p=.07, η^2=0.086) and it was clear that all groups, except for the ADHD group performed better in mental state stories than physical stories.

In order to test the hypothesis that individuals with ASD would show poorer performance in the Strange Stories task, the two groups with ASD (i.e. pure ASD and the comorbid group) were combined into one group with ASD (N=43) and compared to the ADHD (N=20) and control (N=19) groups (Figure 6-7).

No significant group differences were found in physical stories ($F_{(2,79)}$=.50, p=.60, η^2=0.013), yet again a significant group difference was found in mental state stories ($F_{(3,78)}$=2.54, p=.01, η^2=0.103). The post-hoc tests showed that the control group performed better than the ADHD group (p=.003, d=.97). Their performance was also better than the group with ASD; however, the difference between groups did not reach significance (p=.08, d=.50 with the power=.45 for a .05 two-sided level of significance). Moreover, the group with ASD performed better than the

ADHD group in mental state stories, but the difference between groups did not reach significance (p=.08, d=.47 with the power=.40 for a .05 two-sided level of significance).

Again, significant group differences in mental state stories were still observed after controlling for age ($F_{(2,78)}$=5.82, p=.004, η^2=0.130), with the post-hoc tests showing a significantly better score in controls than ADHD (p=.001) and combined group with ASD (a non-significant trend: p=.06); however, when adjusted for VIQ, the group differences in mental state stories disappeared ($F_{(2,78)}$=.96, p=.39, η^2=0.024). Furthermore, both age and VIQ were entered as covariates. The findings were similar to the time only VIQ was entered (as the findings did not change after controlling for age and VIQ, the statistics were not reported).

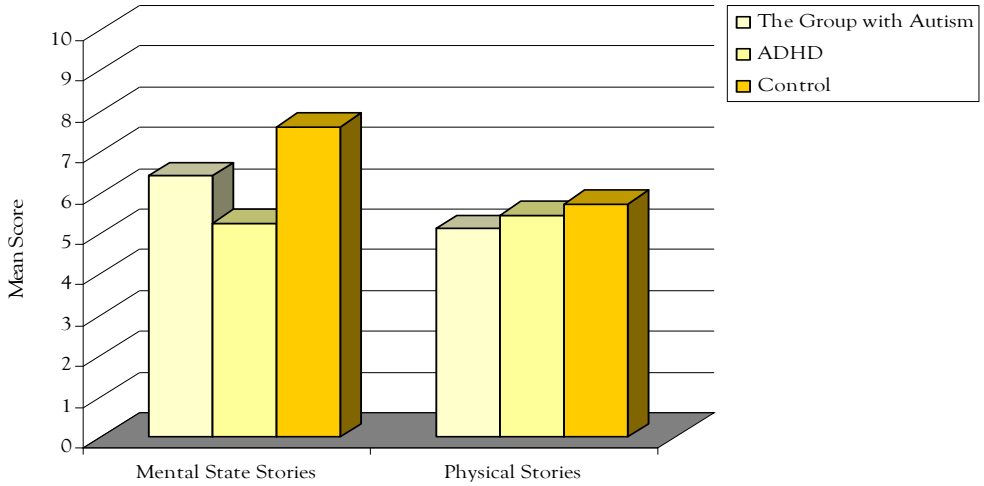


Figure 6-7: Mean Score on Strange Stories Task (Mental State vs. Physical) in group with ASD vs. ADHD and Controls

Table 6-9: Group Comparisons on Strange Stories Task: Means (SD)

	ASD (N=13)	ADHD (N=20)	Comorbid (N=30)	Control (N=19)	Group effect	
					$F_{(3,78)}$	P
Mental State Stories Score (range 0-10)	6.46(2.85)	5.25(2.55)	6.40(2.34)	7.63(2.36)	2.99	.04
Physical Stories Score (range 0-10)	5.08(2.50)	5.45(2.35)	5.13(1.91)	5.74(2.77)	.33	.81

Table 6-10: Effect Sizes (d) of the Strange Stories Task

	Control-ASD	Control-ADHD	Control-Comorbid	ASD-ADHD	ASD-Comorbid	Comorbid-ADHD
Mental State Stories Score	.45	.97	.52	.45	.02	.47
Physical Stories Score	.25	.11	.26	-.15	-.02	-.15

6.10.2.5.2 Effects of Age and IQ

Table 6-11 shows the correlation between the Strange Stories task variables, age and VIQ across all groups. Overall, age was significantly correlated with both types of stories indicating better performance in the older group, whereas VIQ was only correlated with the mental state stories.

Table 6-11: Correlation between Strange Stories Task measures, Age and IQ across all Groups

	Mental State Stories Score	**Physical Stories Score**
Age	.26**	.59**
VIQ	.45**	.14

*** Correlation is significant at the 0.01 level*

Analysis of correlation was then conducted within each group (Table 6-12).

In the control group, there was only a significant correlation between task performance and age (r=.50, p=.01 for mental state stories score; r=.64, p=.002 for physical stories score) and the task performance in this group was independent of VIQ.

In the ASD group, there was only a significant correlation for the mental state stories score with VIQ (r=.73 p=.002). A significant correlation was also observed between the physical stories score and VIQ (r=.54, p=.03). A moderate correlation was observed between the age and physical stories score which did not reach significance (r=.39, p=.09).

In the ADHD group, age was significantly correlated with both types of stories (r=.36, p=.04 for mental state stories score; r=.73, p<.001 for physical stories score).

Finally, in the comorbid group, age was only significantly correlated with the physical stories score (r=.56, p=.001).

Even though the effect of VIQ on the task performance appeared to be more pronounced in the ASD group, when the magnitude of correlations was explored by Fisher's r-to-z transformation, no differences between the groups were observed (all p>.05). Moreover, the effect of age on the Strange Stories performance was relatively the same between groups (all p>.05).

Table 6-12: Correlation between Strange Stories Task measures, age and VIQ across all groups

	Mental State Stories Score		Physical Stories Score	
	Age	**VIQ**	**Age**	**VIQ**
ASD	.13	.73**	.39	.54*
ADHD	.36	.30	.73**	.04
Comorbid	.21	.28	.56**	-.07
Control	.50*	.18	.64**	.05

** Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level.*

6.10.2.5.3 Correlation between Task Measures

Across all groups, there was a significant correlation between mental state stories score and physical stories score (r=.43, p<.001), which is not surprising as both scores are a reflection of participants' abilities in story comprehension regardless of story content. The same pattern of correlation was observed within each group.

6.10.2.5.4 Correlations between Task Measures and Clinical Measures

In order to address whether performance in the Strange Stories task was related to clinical measures of ASD and ADHD behaviours, further analyses were carried out with the clinical measures including Conners score, SCQ and selective scores of SDQ (SDQ total score and SDQ hyperactivity) across the groups (see Table 6-13) and in each group (Table 6-14).

Table 6-13: Correlation between Strange Stories Task measures and clinical measures across all groups

	Conners Inattention	Conners Hyperactivity /Impulsivity	SCQ	SDQ Total	SDQ Hyperactivity
Mental State Stories	-.32**	-.14	-.15	-.22	-.27*
Physical Stories	-.31**	-.04	-.10	-.10	-.17

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level*

Analysis of correlation was then conducted within each group: In the control group, a moderate correlation was observed between Conners inattention and both the mental state stories score (r_s=-.40, p=.04) and the physical stories score (r_s=-.45, p=.03).

The ADHD group showed a relatively high correlation for SDQ hyperactivity and mental state stories score (r=-.68, p=.002) which remained significant after controlling for the effects of age and VIQ.

In the combined group with ASD, there was a significant correlation between Conners inattention and physical stories score (r_s=-.34, p=.01) and also between ADOS communication score and physical stories score (r=-.27, p=.04). The latter correlation remained significant after controlling for the effects of age and VIQ.

In the ASD group, there was a significant correlation between the mental state stories score and SCQ (r=-.66, p=.007), indicating higher autistic symptomatology in this group was related to poorer performance in the mental states stories. There was also a significant correlation between the mental state stories score and SDQ total score (r=-.56, p=.04). Moreover, a significant correlation was observed between task measures and ADI communication score (r=-.53, p=.04 for mental state stories score and r=-.60, p=.02 for physical stories score) and also between ADI social score and task variables (r=-.59, p=.02 for mental state stories score and r=-.51, p=.04 for physical stories score). All the above correlations remained significant after controlling for age, but when controlled for VIQ, the significance disappeared.

Finally, in the comorbid group the relationship between the Strange Stories task measures and autistic symptoms as well as ADHD symptoms was assessed. A significant correlation was observed only for the Conners inattention and physical stories score (r_s=-.36, p=.03).

Table 6-14: Correlation between Strange Stories Task measures and clinical measures for each group (Unadjusted for age and VIQ)

	Mental State Stories Score	Physical Stories Score
Controls		
Conners Inattention	-.41*	-.45*
Conners Hyperactivity /Impulsivity	.02	-.25
SCQ	-.04	.06
SDQ Total	-.35	-.38
SDQ Hyperactivity	-.08	-.50
ASD		
Conners Inattention	-.40	-.30
Conners Hyperactivity /Impulsivity	-.06	-.28
SCQ	-.66**	-.43
SDQ Total	-.56*	-.37
SDQ Hyperactivity	-.42	-.36
ADHD		
Conners Inattention	-.24	-.24
Conners Hyperactivity /Impulsivity	-.16	-.06
SCQ	.06	-.10
SDQ Total	-.16	-.16
SDQ Hyperactivity	-.68**	-.42
Comorbid		
Conners Inattention	-.02	-.36*
Conners Hyperactivity /Impulsivity	.21	.28
SCQ	.15	.24
SDQ Total	.16	-.11
SDQ Hyperactivity	.13	.02

**Correlation is significant at the 0.05 level,* ***Correlation is significant at the 0.01 level*

6.10.2.6 Discussion of the Strange Stories Task

The Strange Stories task has been shown to be a sensitive means of testing advanced mentalising abilities in both children and adults with HFA (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Brent, et al., 2004; Happe, 1994a; Kaland, et al., 2005; White, et al., 2009). It has been shown that even those who passed the standard ToM tasks had difficulty with the Strange Stories task and that what distinguished them from the controls was not a failure to use mental state terms, but a failure to use the context-appropriate terms (Happe, 1994a).

This part of the study aimed to replicate the previous findings by revisiting the Strange Stories task in a group of individuals with HFA and to extend previous research by comparing the ASD group to a group of age- and IQ matched ADHD and comorbid groups to test the specificity of the mentalising impairment as evident in this task.

The results showed that all participants performed at the same level on physical (i.e. control) stories and were able to make inferences about physical events. This therefore suggests good text and sentence comprehension in the clinical groups as well as the control group.

This was the first study which investigated the Strange Stories task in individuals with a comorbid diagnosis and showed that the performance in the comorbid group was to a large extent similar to the ASD group in terms of understanding stories with social contents.

The two groups with ASD showed relatively poorer performance in mental state stories compared with controls in terms of accuracy of their responses. Even though the effect sizes of the differences were medium, the differences did not reach significance. This lack of differentiation might be to some extent due to the limited power of the present sample.

However, it seems that the tendency for poorer understanding of mental stories in the two groups with ASD in comparison to controls was mainly mediated by the difference in the verbal ability as the difference disappeared when VIQ was controlled for.

The ADHD group in the current study showed poorer performance in mental state stories compared to controls. This is in contrast to the findings by Charman et al. (2001) that showed an intact performance of individuals with ADHD in Strange Stories task (Charman, et al., 2001) but supports the studies that found mentalising difficulties in the ADHD group (Buitelaar, van der Wees, et al., 1999). However, it is important to note that the difference between ADHD and controls seems to be driven by the lower verbal ability in this group as the difference disappeared after controlling for VIQ.

Interestingly, all groups except for the ADHD group performed better in stories with social content than stories with physical content indicating that physical stories were generally more difficult compared to mental state stories in the present sample. This might suggest a more

generalised attentional problem in the ADHD group which led to poor performance across all stories, independent of the stories' content.

Another aim of the present study was to examine the associations between performance in the Strange Stories task, age, and verbal ability, as these might highlight possible differences between the groups. Developmental improvement was apparent in all groups. Even though the effect of VIQ on the task performance appeared to be more pronounced in the ASD group, no group differences were detected in the magnitude of the correlations. This finding is in contrast to the previous studies that observed a stronger association with IQ and language ability in ASD than control groups in terms of performance in standard ToM measures (Buitelaar & van der Wees, 1997). This has been interpreted by Frith et al. as indicating that the correct responses may be 'hacked out' by ASD individuals, in contrast to the more intuitive solution for typically developing children (Frith, Happe, & Siddons, 1994).

In terms of associations between the tasks, all groups showed within-task intercorrelations between the mental state and physical items on the Strange Stories task, indicating the large shared task demands not specific to the mental and physical reasoning requirements.

Correlation between the task performance and clinical measures revealed that, across the groups, symptoms of inattention were related to greater difficulty in understanding stories, independent of the content. While in the ADHD group, symptoms of hyperactivity were associated with poorer performance on mental state stories, in the ASD group higher autistic behaviours (i.e. social and communication impairments) were related to greater difficulty in understanding stories, independent of the content. In the comorbid group, it was found that inattentiveness was related to poorer understanding of the physical stories. These findings therefore suggest that different factors in each group contribute to the task performance.

6.10.2.7 Conclusion

The current study extends previous research by comparing the ASD group to a group of age- and IQ-matched controls. It is the first to compare the performance of individuals with ASD with individuals with ADHD in the Strange Stories task and to take into account the co-occurrence of the symptoms of ADHD and ASD when comparing the two groups.

It was observed that all groups performed at the same level in physical stories, suggesting an intact text and sentence comprehension in the clinical groups similar to the control group. The ADHD group showed poorer performance; and the two groups with ASD showed a tendency for poorer understanding of mental state stories compared to controls; however, the group differences appeared to be mainly due to differences in cognitive and verbal ability.

6.10.2.8 Limitations and Suggestions for Future Research

There were a number of limitations: First, as this task was introduced later during the study, the sample size was small and unequal, and the participants' age range was quite wide. In addition, the number of stories used was relatively low compared to previous studies. Furthermore, some of the previous studies adopted a more detailed scoring system; for example, they scored the stories quantitatively and qualitatively (i.e. both in terms of the number of mental states attributed and appropriateness) (Happe, 1994a) or they added alternative control stories such as physical-animal stories (White, et al., 2009).

It is suggested that future research reassess the Strange Stories task performance of individuals with ASD in comparison to alternative control groups such as ADHD using a larger sample and more stories in both mental and physical contexts. It is also recommended that they consider the co-occurrence of ADHD in their ASD group in order to control for its confounding effect.

It is also recommended that the descriptions provided by the participants be further examined qualitatively as well as quantitatively. This would possibly help to capture the elements that distinguish the individuals.

6.10.3 Experiment 3: Cueing Task

The attentional mechanism corresponding to reflexive orienting towards the direction of other's eye gaze was directly assessed using a Posner-style spatial cueing paradigm, 1980 (Posner, 1980). In cueing paradigms, participants are asked to detect visual targets, which may appear on either side of a visual fixation point. Before the target appears, a stimulus cues the participant to one side or the other.

Many studies have assessed the performance of ASD individuals using a cueing paradigm in order to examine their sensitivity to social cues; however, comparisons have only been made to typically developing groups and studies comparing the ASD group with alternative, clinical comparison groups are lacking.

The Social vs. Non-Social Cueing Task reported on here, was designed in order to investigate whether children and adolescents with ASD shift their spatial attention in the direction of perceived eye gaze or an arrow differently, and to assess how the performance of individuals with ADHD compares to that in individuals with ASD in this task.

6.10.3.1 Aims

In this part of the study, an overt gaze cueing paradigm was employed in which eye movements were recorded by an eye-tracker in order to determine whether high-functioning children with ASD show differences in gaze cueing compared to controls. This task has also investigated whether possible abnormalities in orienting of attention are specific to gaze cues, or whether they are present in response to symbolic cues, such as arrows. Moreover, the pattern of

behaviour in a cueing paradigm has been assessed and reported in individuals with ADHD and comorbid ASD-ADHD for the first time.

Using eye tracking in the cueing paradigm has several advantages over standard covert cueing tasks as it offers a rich data set. While in the standard covert cueing task RT is measured indirectly (e.g. pressing a response key), when using an eye-tracker saccadic reaction times (SRTs) are recorded directly. Therefore, SRTs are a more direct measurement of attention allocation. Eye tracking provides information about the timing, the direction of saccades for saccades correctly executed toward the target, as well as the error responses.

6.10.3.2 Method

The experiment was modelled after Senju's task (Senju, et al., 2004). The task was carried out in two blocks, with a break after the first one. It comprised 72 trials in total, and lasted for 5 minutes. The first block included 48 trials and the second block consisted of 24 trials. In each block, half of the trials contained social cueing (gaze-cue trials) and the rest non-social cueing (arrow-cue trials).

Each trial began with a centrally presented black circle (location at 0°), subtending around 0.5° x 0.5° as a fixation point (FP) which remained on the screen for 300msec. The pre-cueing stimulus then appeared at the centre of the screen for 600msec, which was then replaced by a cueing stimulus. A black & white photo of a female face (borrowed from Professor Bruce Hood) was used as a pre-cueing stimulus in gaze-cue trials. The same basic image was used to produce both the left- and right-gazing faces (averted gaze) used as the social cue. The images of the faces measured 2.5° wide and 4° high. A small greyscale bar measured 1.5° wide and 0.7° high and was used as a pre-cueing stimulus in arrow-cue trials. The non-social cue was a greyscale arrow pointing to the left or right. The arrow measured 1.5° wide and 1.2° high.

In all trials, after the FP, the pre-cueing and then either the face looking right/left or the arrow pointing to the right/left was presented. The peripheral target consisted of a small black circle subtending around 0.5° x 0.5°, positioned (±15°), presented randomly either to the right or the left of a cue within 300, 600 or 900mesc after the onset of the cue (see Figure 6-8 for an example of a gaze-cue and arrow-cue trial). All stimuli were presented against a white background. The target remained displayed until the participant looked at it or until 800msec elapsed. Different stimulus onset asynchronies (SOA; 300, 600, or 900 msec) were chosen to make the target onset temporally unpredictable.

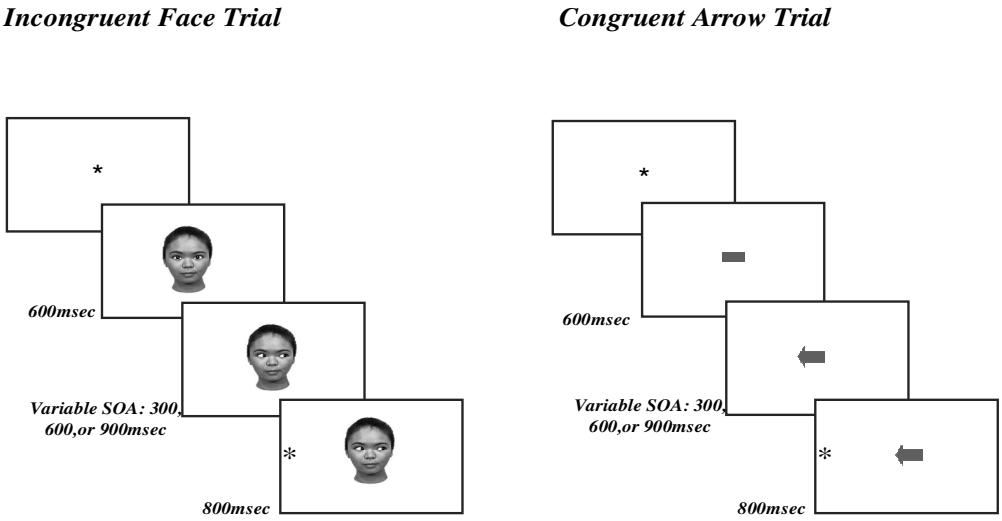


Figure 6-8: Sequence of events for an Incongruent Gaze Trial and a Congruent Arrow trial

There were two within-participant factors: cue type (eye gaze versus arrow), and cue congruency (congruent versus incongruent). Cue type/congruency and all SOA durations were presented randomly and equally within each block. The cue was non-predictive for both social and non-social cues (the directions of both the gaze and the arrow are completely irrelevant to the target position- i.e., cue is predictive only in 50% of trials). Following a study by Ristic et al (Ristic, et al., 2005), the condition in which there is an overlap between the cue and the target was chosen.

6.10.3.3 Procedure

The task was administered in the same situation as described in section 5.7.2.1.1. for prosaccade and antisaccade tasks. Eye movements were monitored using an Eyelink 1000 eye-tracker (SR Research) and eye movements were recorded monocular at 1000HZ.

Participants were asked to fixate on the FP and the experimenter initiated the trial by pressing a key on the host computer once the participant had achieved fixation. The Eyelink 1000 displays participants' fixation points on a separate (host) monitor that the experimenter views during the experiment. It was therefore very clear on a trial by trial basis whether the central fixation point was fixated prior to each trial being initiated by the experimenter. If it was not then the participant was recalibrated before testing resumed. Participants were instructed as follows: *'At the beginning, you will see a small circle on the screen. Please look at the circle. Then you will see either a face or a bar. After a while, the face will look to the right or the left and the bar will change to an arrow pointing right or*

left. There will then be a small circle on the side, either right or left. Please look at the circle as fast as you can. Please keep your head as still as you can'.

In order to familiarise participants with the task requirements, 6 practice trials were carried out before each task, which were repeated if necessary. Performance was monitored by the experimenter; participants were provided with verbal feedback on their performance during and after the practice trials. No feedback was given during experimental trials.

6.10.3.4 Data Analysis

Saccadic velocities, amplitudes, and latencies were determined by using an interactive computer analysis program that displayed each trial for review by the experimenter (the Data Viewer package; SR Research). Data recorded for each individual on each task were then evaluated on a trial-to-trial basis. Saccade latency was defined as the time, in milliseconds, from target appearance to saccade initiation.

Criteria for saccade analysis in the cueing task were set as follows:

1) The minimum amplitude was set as *2 degrees*. Saccades with an amplitude lower than 2º were removed and not included for further analysis.

2) If at the cue onset the eye was more than *50 pixels* off centre, the trial was deleted.

3) Trials in which no saccadic response was made or in which the saccadic response occurred after disappearance of the target were ignored

4) If there was a blink between *-100msec* and *+70msec* of the target onset, the trial was deleted.

5) Only saccade latencies of greater than *70msec* after the target onset were included in the analyses (i.e. *correct saccade*).

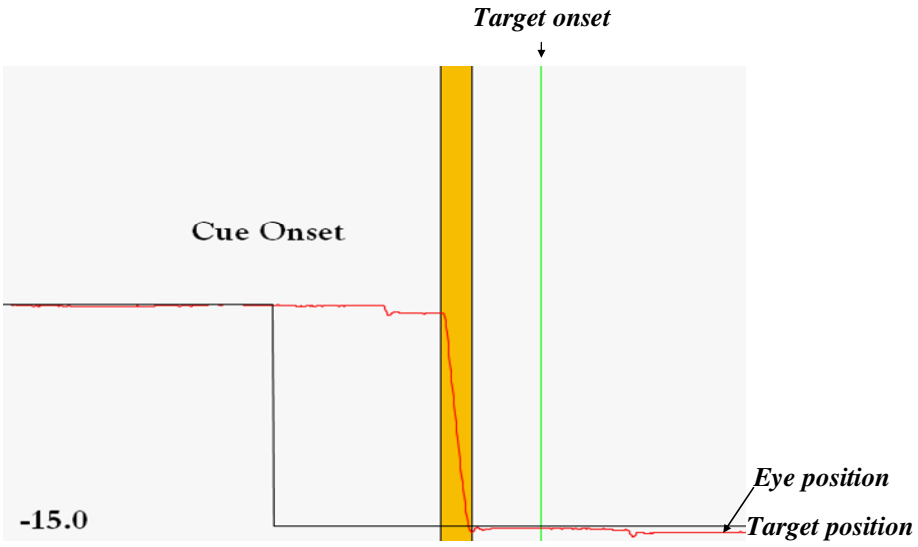
6) If there was a clear saccade of greater than *70msec* after the target was contaminated by a blink, the saccade was retained but its metrices (like amplitude and velocity) were deleted.

As the Cueing task involved the simultaneous study of two independent factor variables, factorial design was used. A repeated measure ANOVA with groups as the between-subjects factor and different conditions (Congruent versus Incongruent; Gaze versus Arrow) as the within-subjects factor was employed to assess any interactions between groups and tasks.

The cue period was defined as the time duration between the cue onset and target onset. Performance variables included: Saccadic Reaction Time (SRT), saccade amplitude, saccade velocity, the percentage of anticipatory saccades, and the correction rate.

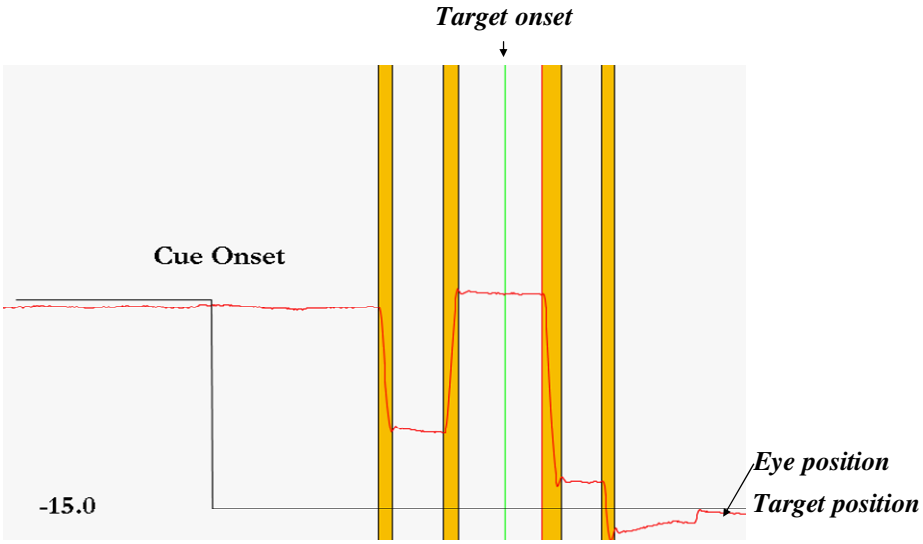
SRT, saccade amplitude, and saccade velocity were measured and reported only for the correct saccades as defined above. SRT (or saccade latency) was defined as the time between the target onset and the initiation of the first saccade in the correct direction.

If there was a saccade *70mSec* after the cue onset until *+70msec* after the target onset, it was considered as a *'Premature response'* or *'Anticipatory saccade'* (see Figure 6-9). In case of an anticipatory saccade, if the anticipation was then corrected either in the cue period or after the target onset (in the time window of *0* to *+70msec)*; it was counted as a correction (see Figure 6-10). The correction of the premature responses could occur either during the cue period or after the target onset (in the time window of *0* to *+70msec*).



Legend: x-axis, time (ms); y-axis, degree of visual angle

Figure 6-9: An Example of a Cueing Trial with an Anticipatory Saccade



Legend: x-axis, time (ms); y-axis, degree of visual angle

Figure 6-10: An Example of a Correct Cueing Trial with an Anticipatory Saccade and a Correction Saccade

6.10.3.5 Hypotheses

Given the difficulty individuals with ASD have in gaze following behaviours (reviewed above, see sections 6.7.1 and 6.7.3), it was predicted that whilst the control group would demonstrate equal cueing effects for arrow and eye gaze cues, ASD participants would show diminished salience of social stimuli and thus stronger cueing effects for arrow than for eye gaze cues. Also, it was predicted that those individuals with more symptoms of ASD, specifically in social and communication domains would show less sensitivity to eye gaze cue.

As individuals with ADHD are expected to show more generalised attentional problems, it was predicted that this group would show diminished salience of both cues, independent of their type compared to the control group. It was moreover predicted that while individuals with ASD would show diminished salience of social stimuli, individuals with ADHD would show less sensitivity in response to both social and non-social cues.

This is the first study to evaluate performance on a cueing task in individuals with a diagnosis of comorbid ASD and ADHD. Therefore, exploratory analyses were conducted to investigate whether participants in the comorbid group showed a different pattern of performance compared to control and pure groups.

6.10.3.6 Results from Cueing Tasks

6.10.3.7 Piloting the Experiments

The cueing task was a novel task, designed for the purpose of the current investigation. Therefore, it was first piloted with a group of 10 healthy adults to ensure the feasibility of the tasks, i.e., to see if the instructions were easily understood, and to assess the time duration of each task when presented to the individual (including time required to calibrate the system). In the pilot study, the cueing effect was observed for both gaze and arrow stimuli which indicated that both tasks met the requirements of a standard cueing paradigm.

6.10.3.8 Findings from the Main Study

From the total of 120 individuals, data on the cueing task was available for 111 individuals including 17 ASD, 34 ADHD, 38 comorbid, and 22 controls. 4 of the participants (2 from the ASD group and 2 from the comorbid group) met exclusion criteria for the eye tracking tasks as described in Chapter 3, section 3.2.1.2.

5 participants (including 1 individual from the ADHD group, 2 from the comorbid group, and 2 from the controls) refused to perform the tasks.

Table 6-15 presents demographic information by group for participants who completed the cueing task.

No significant differences in age among the groups (p>.05) were observed. However, significant differences were found for FSIQ, PIQ, and VIQ (all p<.05). Further analysis showed that the two groups of children with ADHD symptomatology (pure ADHD and comorbid groups) had a significantly lower FSIQ, PIQ, and VIQ compared to controls (LSD post-hoc tests, p<.05). Moreover, the ADHD group had a significantly lower FSIQ, and VIQ (LSD post-hoc tests, p<.05), but not PIQ (p>.05), relative to the ASD group. However, no differences between the ASD and comorbid groups were observed, and the ASD group did not differ from controls in FSIQ, PIQ, and VIQ (all p>.05).

Table 6-15: Group descriptive for participants who completed the Cueing Task: Means (SD), [Range]

	ASD (N=17)	**ADHD (N=34)**	**Comorbid (N=38)**	**Controls (N=22)**	**$F_{(3,107)}$**	**P**	**Post-hoc LSD**
Age in month **[Range]**	133.41 (20.77) [96-168]	131.71 (32.19) [84-191]	128.13 (25.18) [87-200]	128.09 (29.77) [91-180]	.22	.88	
FSIQ **[Range]**	113.71 (14.39) [89-139]	101.44 (13.63) [70-135]	106.32 (13.15) [79-142]	121.27 (13.06) [102-149]	10.84	<.001	Controls> ADHD, Comorbid* ASD>ADHD*
PIQ **[Range]**	108.94 (13.32) [86-136]	100.03 (12.62) [70-131]	105.00 (13.51) [75-141]	114.73 (12.62) [100-141]	6.02	.001	Controls> ADHD, Comorbid*
VIQ **[Range]**	115.47 (16.82) [93-145]	102.74 (15.96) [75-133]	106.24 (14.41) [85-146]	123.14 (14.76) [99-151]	9.40	<.001	Controls> ADHD, Comorbid* ASD>ADHD*

**Post-hoc test, p<.05*

6.10.3.8.1 Group Comparisons on the Cueing Task

Initially, analyses were conducted without adjusting for age and IQ. Group differences were explored using repeated measure ANOVA with group as the between-subjects factor and cue type (gaze versus arrow) and congruency (congruent versus incongruent) as the within-subjects factor. Table 6-16 shows descriptive statistics (mean and SD) in the cueing task for different conditions.

Further analysis was conducted by combining performance scores for different cue types and congruency measures into one mean score for each variable, for each individual. The mean score then was used to compute effect sizes of pairwise comparisons and compare values between groups (see Table 6-17).

For SRT, no significant group differences were found ($F_{(3,107)}$=.32, p=.81, η^2=0.009). There was a significant main effect of congruency ($F_{(1,107)}$=4.33, p=.04, η^2=0.039), reflecting significantly faster SRTs in congruent trials than incongruent trials and thus demonstrating a typical cueing effect. No significant group by congruency interaction was detected ($F_{(3,107)}$=1.24, p=.30, η^2=0.034), which indicates that the cueing effect was observed in all groups.

The effect of cue type on SRT showed a non-significant trend ($F_{(1,107)}$=3.74, p=.06, η^2=0.034), though all groups were slightly faster in response to arrow than to eye gaze. No significant group by cue type interaction was detected ($F_{(3,107)}$=.95, p=.42, η^2=0.026), which indicates that the effect of cue was the same across the groups. A significant cue by congruency interaction was observed ($F_{(1,107)}$=35.31, p<.001, η^2=0.248), indicating that the cueing effect was stronger for arrow than gaze (cueing effect for arrow=36.45 (54.47), cueing effect for gaze=-14.21 (60.75), p=.01). The cue by congruency by group interaction was not significant ($F_{(3,107)}$=1.06, p=.37, η^2=0.029), reflecting the equal influence of different conditions for each group. Figure 6-11 depicts SRT for different cue types in congruent and incongruent conditions.

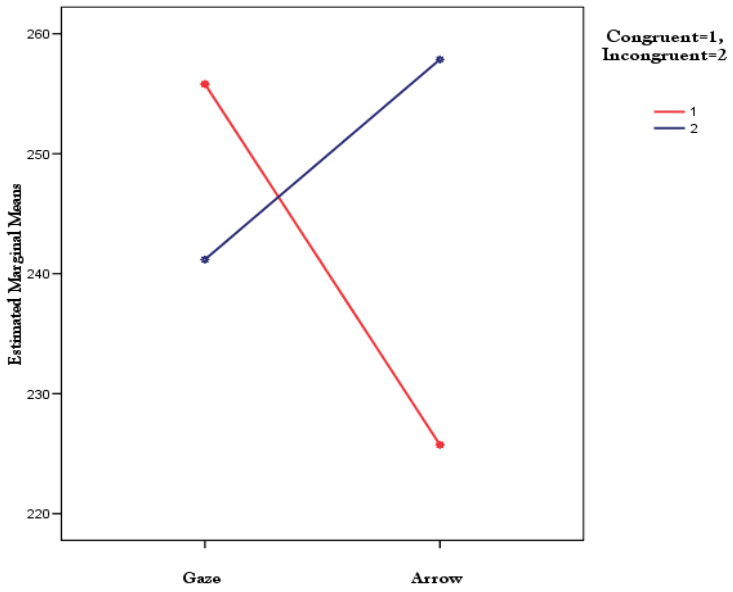


Figure 6-11: Cue type by Congruency interaction for SRT

No significant group differences were found for SRT variability ($F_{(3,106)}$=.33, p=.80, η^2=0.009). There was no significant main effect of congruency ($F_{(1,106)}$=1.98, p=.16, η^2=0.018) or cue type ($F_{(1,106)}$=1.62, p=.20, η^2=0.015) and no significant group by congruency by cue type was detected ($F_{(3,106)}$=.51, p=.68, η^2=0.014).

For amplitude, a significant between group difference was found ($F_{(3,107)}$=3.19, p=.03, η^2=0.082). Post-hoc tests showed significantly bigger amplitude in the control group compared to each of two clinical groups (p=.003 for ADHD-control, and p=.03 for comorbid-control comparisons) and a non-significant trend for the ASD-control comparison (p=.06). There was also a significant main effect of congruency ($F_{(1,107)}$=45.60, p<.001, η^2=0.299), reflecting that amplitudes on congruent trials were significantly smaller than incongruent trials. No significant group by congruency interaction was detected ($F_{(3,107)}$=.51, p=.67, η^2=0.014), which indicates that the cueing effect was observed in all groups.

The effect of cue type on amplitude was significant ($F_{(1,107)}$=3.67, p=.01, η^2=0.056), reflecting larger amplitudes in gaze trials than in arrow trials; however, no significant group by cue type interaction was detected ($F_{(3,107)}$=1.15, p=.33, η^2=0.031). Moreover, there was a significant cue by congruency interaction ($F_{(1,107)}$=15.81, p<.001, η^2=0.129), reflecting a greater difference in amplitude between congruent and incongruent conditions for arrow than gaze. The pattern was the same across groups; the cue by congruency by group interaction was not significant ($F_{(3,107)}$=.79, p=.50, η^2=0.022).

Figure 6-12 depicts the percentage of anticipatory saccade for different cue types in congruent and incongruent conditions. The percentage of anticipatory saccade showed a non-significant trend for group differences ($F_{(3,107)}$=2.34, p=.08, η^2=0.062) with the ADHD group showing a

higher percentage of anticipation compared to the ASD group and controls. There was a significant main effect of congruency ($F_{(1,107)}$=18.93, p<.001, η^2=0.150), showing that the percentage of anticipation was higher in the incongruent trials. No significant group by congruency interaction was detected ($F_{(3,107)}$=1.52, p=.21, η^2=0.041).

The effect of cue type on the percentage of anticipatory saccade was also significant ($F_{(1,107)}$=20.22, p<.001, η^2=0.159), showing that anticipations in arrow trials were significantly more frequent than in gaze trials. However, no significant group by cue type interaction was detected ($F_{(3,107)}$=.12, p=.95, η^2=0.003). No significant cue by congruency interaction was observed (p>.05) and the cue by congruency by group interaction showed a trend towards significance ($F_{(3,107)}$=2.39, p=.07, η^2=0.063).

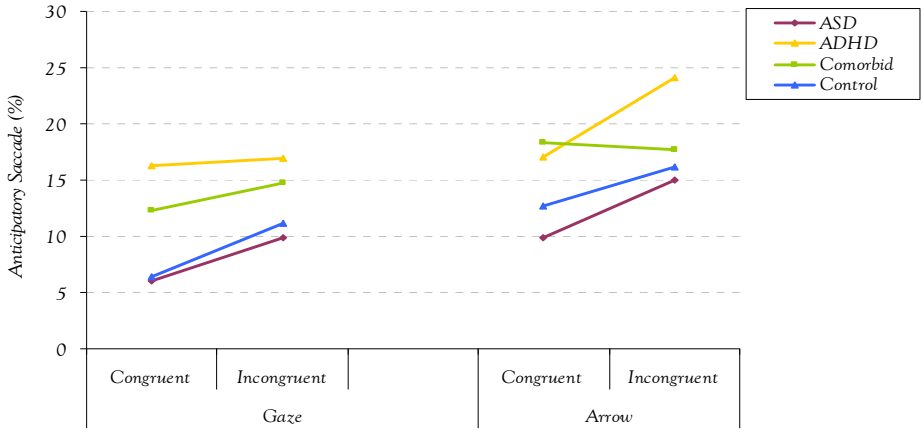


Figure 6-12: Percentage of Anticipatory Saccades for different cue types in congruent and incongruent conditions

The percentage of anticipatory saccade was higher in the two groups with ADHD (i.e. the ADHD and comorbid group) than in the ASD and control groups, though the differences did not reach statistical significance. Effect sizes for pairwise comparisons were calculated: a large effect size of the difference was observed between ADHD and ASD (d=.75) groups and a medium effect size of the difference was observed between comorbid and ASD groups (d=.44); however, the power of these analyses was limited for a .05 two-sided level of significance (power=.73 and power=.36; respectively). Moreover, the effect sizes of the differences between controls and ADHD, and controls and the comorbid group were medium (d=.59 and d=.31, respectively). Yet again, the power of these analyses was limited for a .05 two-sided level of significance (power=.59 and power=.23, respectively).

The correction rate during the cue period showed no significant group differences ($F_{(3,51)}$=.86, p=.46, η^2=0.048). There was no significant main effect of congruency or cue type ($F_{(1,51)}$=.55, p=.65, η^2=0.032 for congruency and $F_{(1,51)}$=.007, p=.93, η^2=0.001). Moreover, no significant cue by congruency interaction was observed (p>.05) and the results showed that all groups were

equally influenced by different conditions as the cue by congruency by group interaction was not significant ($F_{(3,51)}$=1.05, p=.38, η^2=0.058). Medium effect sizes of the difference were observed between control and ASD (d=.51) and also between comorbid group and ASD groups (d=.41); however, the power of these analyses was limited for a .05 two-sided level of significance (power=.13 and power=.14; respectively). Moreover, the effect sizes of the differences between control and ADHD, and comorbid and ADHD groups were medium (d=.50 and d=.42, respectively). Yet again, the power of these analyses was limited for a .05 two-sided level of significance (power=.26 and power=.27, respectively).

No significant group differences were found for the correction rate after the target onset in either gaze trials ($F_{(3,80)}$=.62, p=.60, η^2=0.023) or arrow trials ($F_{(3,85)}$=.27, p=.85, η^2=0.009).

All the above analyses were repeated adjusting for age and FSIQ. ANCOVA was run on the task variables with group as the between-subjects variable and age and FSIQ as covariates. When adjusted for age and VIQ, separately, the findings did not substantially differ from the analysis unadjusted. Furthermore, age and FSIQ were entered as covariates together. Again, no differences were observed from the unadjusted analysis (as the findings did not change after controlling for age and VIQ, in order not to be repetitive the statistics were not reported).

Table 6-16: Group comparisons on Cueing task: Means (SD)

	Cue Type	Congruency	ASD (N=17)	ADHD (N=34)	Comorbid (N=38)	Control (N=22)
Saccade Latency (msec)	**Gaze**	**Congruent**	247.56 (51.07)	257.13 (59.51)	261.16 (84.02)	257.37 (54.83)
		Incongruent	235.36 (53.30)	237.35 (43.37)	254.04 (48.47)	237.97 (51.82)
	Arrow	**Congruent**	241.55 (58.94)	217.04 (58.30)	222.29 (57.50)	222.08 (50.79)
		Incongruent	250.63 (52.04)	259.36 (48.38)	269.58 (59.74)	251.87 (49.36)
Saccade Amplitude (º)	**Gaze**	**Congruent**	13.85 (1.08)	13.66 (.81)	13.75 (1.02)	14.26 (1.08)
		Incongruent	14.11 (.85)	13.90 (.75)	14.15 (.73)	14.34 (.78)
	Arrow	**Congruent**	13.48 (.96)	13.11 (.88)	13.40 (.87)	13.97 (1.04)
		Incongruent	13.96 (1.45)	13.99 (.98)	14.15 (1.06)	14.72 (1.15)
Anticipatory Saccade (%)	**Gaze**	**Congruent**	6.05 (9.96)	16.27 (13.81)	12.35 (16.14)	6.43 (7.78)
		Incongruent	9.91 (14.20)	16.94 (14.68)	14.74 (16.52)	11.18 (10.78)
	Arrow	**Congruent**	9.86 (13.11)	17.11 (12.97)	18.34 (15.35)	12.69 (15.25)
		Incongruent	15.05 (14.43)	24.07 (15.69)	17.65(16.69)	16.20 (16.74)
Correction Rate in the Cue Period (%)	**Gaze**	**Congruent**	10.71 (21.43)	8.67 (16.38)	22.36 (31.77)	18.52 (33.79)
		Incongruent	12.50 (25.00)	13.20 (19.10)	13.82 (19.75)	15.61 (26.91)
	Arrow	**Congruent**	22.08 (15.11)	16.42 (26.14)	18.04 (25.98)	13.27 (18.62)
		Incongruent	2.50 (5.00)	7.91 (11.71)	15.08 (22.50)	22.35 (18.77)
Correction Rate after Target Onset (%)	**Gaze**	**Incongruent**	84.07 (24.82)	74.45 (32.68)	81.14 (29.26)	70.39 (36.58)
	Arrow	**Incongruent**	82.31 (29.61)	86.25 (19.93)	82.75 (26.39)	79.62 (27.43)

Table 6-17: Effect Sizes (d) of the Cueing Task [a]

	ASD-Control	ADHD-Control	Comorbid-Control	ADHD-ASD	Comorbid-ASD	Comorbid-ADHD
Saccade Latency (msec)	.03	.009	.20	-.02	.16	.20
SRT variability	-.06	.18	.16	.25	.22	-.005
Anticipatory Saccade (%)	-.13	.60	.32	.75	.44	-.21
Saccade Amplitude (º)	-.50	-.81	-.54	-.23	.01	.28
Correction Rate (%) (in Cue Period)	-.51	-.50	-.009	-.03	.41	.42
Correction Rate (%) (after Target Onset)	-.52	-.19	.18	-.36	-.29	.02

a. Effect sizes of pairwise comparisons were calculated for the combined mean scores of different cue types and congruency.

6.10.3.8.2 Effects of Age and IQ

The correlations of the cueing task variables with age and FSIQ were explored. There was a mild correlation between SRT and age (r=-.22, p=.02), reflecting faster SRT in older individuals. Moreover, a significant correlation was observed between SRT variability and age (r=-.37, p<.001). No significant correlation was observed between FSIQ and task variables (p>.05).

Analysis of correlation was then conducted within each group. Table 6-18 shows the correlations of the cueing task variables with age in each group. No significant correlation was observed between FSIQ and task variables in any group (p>.05).

In the control group, a significant correlation was detected for age and SRT (r=-.59, p=.002), and also between SRT variability and age (r=-.82, p<.001). No significant correlation was observed in the ASD group. In the ADHD group, there was a significant correlation between age and the correction rate in the cue period (r=.38, p=.04) and also between SRT variability and age (r=-.30, p=.04). Finally, in the comorbid group, a significant correlation was detected for SRT variability and age (r=-.28, p=<.04).

Figure 6-13 depicts developmental changes in saccade latency in the four groups of participants. Fisher's r-to-z transformation showed that the effect of age on saccade latency was greater in the control group than ADHD group (z=1.95, p=.05). No differences in the magnitude of correlation were observed between control and ASD groups (z=1.81, p=.07), or between control and comorbid groups (z=1.77, p=.07). No differences in the magnitude of the correlation coefficients were observed between the clinical groups (all p>.05).

For SRT variability, the magnitude of the correlation coefficients was greater in the control group than ASD (z=2.85, p=.004), ADHD (z=2.91, p=.004) and comorbid groups (z=3.05, p=.002). No differences in the magnitude of the correlation coefficients were observed between the clinical groups (all p>.05). Figure 6-14 depicts developmental changes in saccade latency in the four groups of participants.

For anticipatory saccade, saccade amplitude, and correction rate (either in the cue period or after target onset) no difference in the magnitude of the correlation coefficients between the groups was detected by Fisher's r-to-z transformation (p>.05).

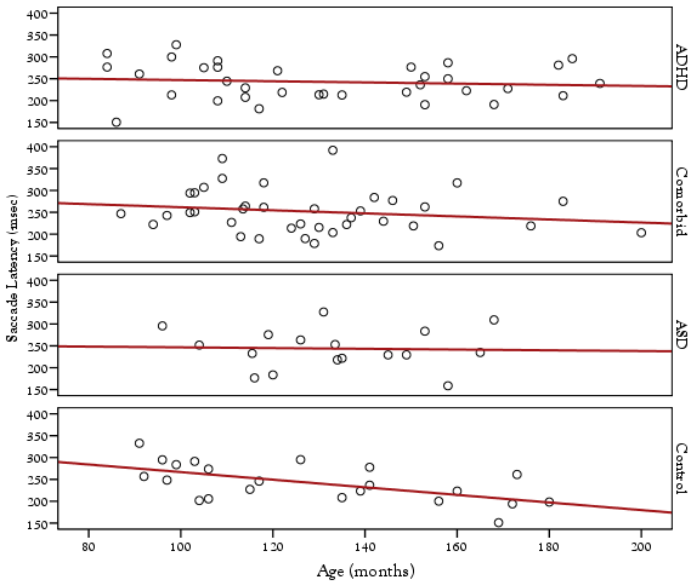


Figure 6-13: Developmental changes in Saccade Latency

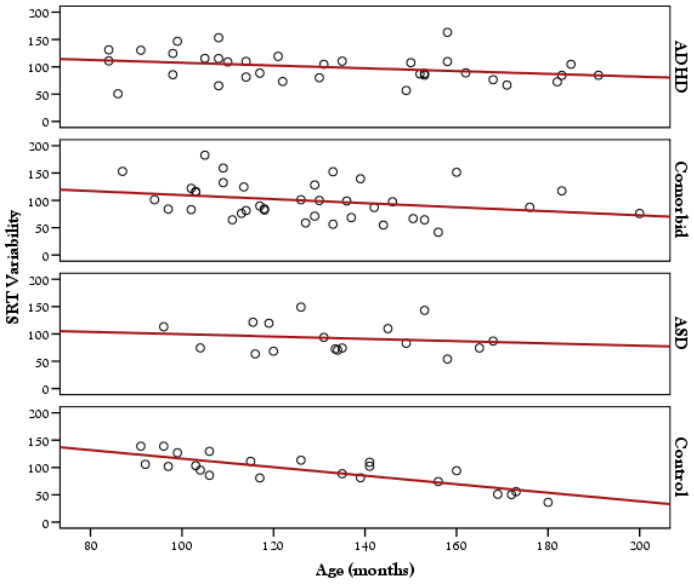


Figure 6-14: Developmental changes in SRT Variability

Table 6-18: Correlation between Cueing Task measures and age by group

	Age* Latency	Age* SRT Variability	Age* Anticipatory Saccade	Age* Amplitude	Age* Correction Rate in Cue Period	Age* Correction Rate after Target onset
ASD	-.04	-.15	.21	-.17	-.14	-.17
ADHD	-.11	-.30*	.25	.16	.38*	.05
Comorbid	-.17	-.28*	.25	.13	-.06	-.23
Control	-.59**	-.82**	-.28	-.07	.06	-.06

**Correlation is significant at the 0.05 level,* ***Correlation is significant at the 0.01 level*

6.10.3.8.3 Correlation between Task Measures and Clinical Measures

Correlations between Cueing task measures and clinical measures including Conners score, SCQ and selective scores of SDQ (SDQ total score and SDQ hyperactivity) were assessed across the groups (see Table 6-19). Analysis of the correlations was then conducted within each group (see Table 6-20).

Table 6-19: Correlations between Cueing Task measures and clinical measures across all groups

	Conners Inattention	Conners Hyperactivity /Impulsivity	SCQ	SDQ Total	SDQ Hyperactivity
Saccade Latency (msec)	.05	.08	-.006	.002	-.06
SRT Variability	.14	.15	-.09	.06	.14
Saccade Amplitude (º)	-.19*	-.18*	-.18*	-.32**	-.33**
Anticipatory Saccade (%)	.16*	.20*	.05	.18	.22*
Correction Rate in the Cue Period (%)	-.19	-.12	-.03	-.03	.05

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level*

In the control group, there was only a significant correlation between Conners inattention score and the percentage of anticipatory saccade (r_s=.39, p=.04). Moreover, a significant correlation was observed between SRT variability and SCQ score (r=.41, p=.03), reflecting the more variable responses in those with more ASD traits. However, the significance disappeared after covarying for age and FSIQ.

In the ASD group, a significant correlation was observed between the percentage of anticipatory saccade and SDQ total score (r=.48, p=.04) and SDQ hyperactivity subscale (r=.55, p=.02), which both remained significant when the effect of age and FSIQ were corrected for. No correlation was found between Cueing task measures and symptoms of ASD as measured by SCQ, ADOS, and ADI-R separately).

In the ADHD group, there was a significant correlation between the Conners hyperactivity score and saccade latency (r_s=.30, p=.04) and SRT variability (r_s=.40, p=.01), reflecting slower and more variable responses in those with more severe symptoms of hyperactivity/impulsivity. Moreover, a significant correlation was observed between saccade amplitude and SDQ total score (r=-.33, p=.04), suggesting a smaller amplitude in those with a higher SDQ score.

Finally, in the comorbid group, a significant correlation was found between SCQ and saccade latency (r=.32, p=.02), which remained significant even after the effects of age and FSIQ were controlled for.

Table 6-20: Correlations between Cueing Task measures and clinical measures for each group (Unadjusted for age and FSIQ)

	Latency	SRT Variability	Anticipatory Saccade	Amplitude
Controls				
Conners Inattention	-.11	.09	.39*	.05
Conners Hyperactivity/Impulsivity	.03	.28	.17	.25
SCQ	.30	.41*	.12	-.29
SDQ Total	-.07	.23	.13	.06
SDQ Hyperactivity	.06	.29	.60*	.25
ASD				
Conners Inattention	-.20	-.14	-.13	-.20
Conners Hyperactivity/Impulsivity	.40	.24	-.39	-.20
SCQ	.08	-.03	.05	-.35
SDQ Total	.06	.18	.48*	-.28
SDQ Hyperactivity	-.20	.28	.55*	-.69**
ADHD				
Conners Inattention	.06	.18	.04	-.11
Conners Hyperactivity/Impulsivity	.30*	.40**	.17	.07
SCQ	-.08	-.26	-.16	.18
SDQ Total	-.13	-.07	.07	-.33*
SDQ Hyperactivity	-.12	-.01	-.05	-.27
Comorbid				
Conners Inattention	.20	.24	-.10	.08
Conners Hyperactivity/Impulsivity	.06	.07	.08	-.19
SCQ	-.32*	-.12	.09	-.11
SDQ Total	.14	.04	-.09	-.22
SDQ Hyperactivity	-.05	.17	-.19	-.26

**Correlation is significant at the 0.05 level,* ***Correlation is significant at the 0.01 level*

6.10.3.9 Discussion of the Cueing Tasks

In this part of the study, the aim was to examine whether high functioning children and adolescents with ASD differed from controls in their sensitivity to social cues such as eye gaze compared to non-social cues such as an arrow. Moreover, saccadic eye movements of the ADHD and comorbid groups during the cueing task were assessed in order to investigate their response pattern to social versus non-social cues. The study is the first to employ this design.

There are a few studies which have explored overt attention using a cueing paradigm by measuring saccadic reaction time (SRT) in ASD (Kuhn, et al., 2010), but the majority of the previous studies have measured motor RTs (i.e. participants had to respond by pressing a response key). In the current study, the use of an Eye Tracker to measure overt attention enabled this experiment to have the potential to reveal subtle differences in attentional orienting in ASD, not apparent in simple RT tasks.

6.10.3.9.1 Differences between Controls and Clinical groups in the Cueing Task

Contrary to expectations, the findings of the current study showed no evidence for deficits in attentional orienting to social stimuli in children and adolescents with ASD as they did not differ in their SRT to different cue types (i.e. eye gaze and arrow) from controls. This is in line with studies that reported the same pattern of response in controls and ASD groups (Ames & Jarrold, 2007; Kuhn, et al., 2010; Kylliainen & Hietanen, 2004; Pruett, et al., 2011; Swettenham, et al., 2003), but contrasts with those that found a greater salience to social cues in the control group than ASD groups (Chawarska, et al., 2003; Ristic, et al., 2005; Senju, et al., 2004).

One explanation for the different findings from those by Senju and Ristic which found different response patterns in ASD group from controls (Ristic, et al., 2005; Senju, et al., 2004) could be the fact that they measured the motor RT without assessing whether the motor coordination was intact in their ASD group. Since, as mentioned earlier, motor coordination problems have been reported in individuals with ASD (Murray, 2010), this might adversely affect their RT. However, the current study used direct information from eye movement recordings and is not confounded by any underlying motor problems.

The difference of the present study from the study by Chawarska (Chawarska, et al., 2003) could be explained by the differences in the sample characteristics, as Chawarska assessed toddlers with autism (mean age=2.23 years), whereas this study assessed higher-functioning children and adolescents. Therefore, the lack of group differences in the current study might be due to the fact that older and more able individuals with ASD may learn some of the social skills which come naturally to controls, such as eye-gaze cueing, and by the time they reach childhood these differences are less apparent. This also has been suggested by other researchers (Kuhn, et al., 2010; Leekam, Hunnisett, & Moore, 1998). Leekam even proposed that failure to

find deficits in attentional orienting in older individuals with autism does not negate the possibility that deficits did exist earlier in development (Leekam, et al., 1998).

A different finding in the present study from the previous studies was the fact that the cueing effect was observed only in response to the arrow, and not to eye gaze in all groups. All participants were faster in congruent rather than incongruent trials in which an arrow was presented as a central cue even though its direction was not predictive of the target location. This finding, in line with previous studies, suggests that the arrow was orienting attention reflexively (Friesen & Kingstone, 1998; Ristic, et al., 2002; Tipples, 2002). However, the absence of a reflexive shift of attention for the gaze trials contradicts the studies which showed that eye gaze elicited reflexive orienting (Friesen & Kingstone, 1998; Kuhn, et al., 2010; Pruett, et al., 2011; Ristic, et al., 2002; Senju, et al., 2004).

This difference could be partly explained by the difference in the stimulus characteristics used in the current study which was a photo of a face as opposed to the simple schematic face used in some of the previous studies (Friesen & Kingstone, 1998; Kuhn, et al., 2010; Pruett, et al., 2011; Ristic, et al., 2002; Ristic, et al., 2005). As a photo is more complex, it might be more difficult to process. However, this can not account for the discrepancy between the present findings and those of Senju et al. (Senju, et al., 2004) which reported RT facilitation (i.e. a cueing effect) in both ASD and control groups, also using a photo of a face as the social cue. However, as mentioned above, Senju's study differed from the current study in its methodology. They measured the motor RT and not direct information from eye movement recordings.

The study by Kuhn et al. (2010) was the only one which used eye tracking. However, they studied adults and their task was slightly different from this study as they used arrow and gaze as distractors and explicitly instructed their participants to ignore the distractors. They found that both ASD and control groups responded similarly to both types of distractors (eye gaze and arrow); moreover, similar cueing effects were found for both types of distractors in both groups (Kuhn, et al., 2010).

The two groups with ADHD showed the same pattern of response to different cue types as the ASD and control groups: they were slightly faster in the arrow trials than in the gaze trials and they showed a cueing effect only for arrow and not gaze cues.

The fact that all groups were slightly faster on the arrow trials than on the gaze trials and that the arrow but not the eye gaze could elicit reflexive shifts of attention in this study, might have been due to the simplicity of the arrow which made it easier to process and therefore, to respond to. Another possibility is that arrow was more alerting than gaze, eliciting reflexive shift in attention.

Some of the metrics and dynamics of oculomotor control including amplitude were different between the control and clinical groups with medium to large effect sizes with the control group showing a significantly higher amplitude than that in the three clinical groups.

The groups also differed in the percentage of anticipatory saccade, even though the difference was only marginally significant. Possibly due to the limited power, the group differences did not reach significance. A higher rate of anticipatory saccade was observed in the ADHD group than the ASD and control groups with large effect sizes. Moreover, the comorbid group showed a higher rate of anticipation than the ASD and controls with medium effect sizes. This pattern of responding reflects the attitude of individuals with ADHD of being impulsive and having difficulties in waiting, therefore their responses are rather premature and early.

Across all groups, the percentage of anticipation was higher in the incongruent trials, which supports the findings by Kuhn et al. (Kuhn, et al., 2010). The rate of anticipatory saccade was also higher in arrow trials than in gaze trials, possibly suggesting that arrow cues result in automatic gaze following.

6.10.3.9.2 Differences between Clinical Groups

This was the first study to compare groups with ASD and ADHD on a cueing paradigm. Given the difficulty individuals with ASD have in gaze following behaviours, it was predicted that ASD participants would show diminished salience of social stimuli. Moreover, as individuals with ADHD were expected to show more generalised attentional problems, it was predicted that this group would show diminished salience of both social and non-social stimuli.

However, the study did not show any differences between the two groups in terms of sensitivity to a social versus non-social cue. Moreover, the comorbid group performed at the same level of the pure groups in terms of generating saccade and the pattern of engagement and shift of their attention in response to different cue types.

The only difference between the ASD group and the two groups with ADHD was the percentage of anticipatory saccade, which was higher in the ADHD and comorbid groups, but possibly due to the limited power, did not reach significance.

The study also aimed to examine the relationship between task performances and clinical symptoms of participants. Across all groups, the symptoms of inattention and hyperactivity were related to smaller amplitude and a higher rate of anticipation. Moreover, social impairment was associated with smaller amplitude.

In the ADHD group, having more symptoms of hyperactivity related to slower and more variable responses, which is in agreement with previous studies which showed that slow, variable, and inaccurate responding is characteristic of ADHD (van der Meere, et al., 1996) and

in the comorbid group, it was the ASD behaviours which were associated with smaller amplitude.

6.10.3.9.3 Age Effect

Another aim of the study was to explore the age-related changes in the task performance. Some of the tasks' measures were related to the age of the participants, albeit with different strengths. In the present sample, the age effect on saccade latency was greater in the control group than ADHD group. Moreover, the developmental improvement in RT variability was greater in the control group than the three clinical groups. These findings suggest that the normal developmental trajectory seen in the controls might be absent in the clinical groups.

However, it is important to note that cross-sectional investigations such as this study cannot definitively address this issue, and longitudinal studies are needed to confirm the developmental maturation in saccadic eye movements.

6.10.3.10 Conclusion

The current study extends previous research by comparing two groups of participants with neurodevelopmental disorders, ADHD and ASD, to a group of age-matched controls and a group of individuals with a comorbid ASD-ADHD.

The findings of the current study found no evidence in support of children and adolescents with ASD responding more rapidly than controls to social versus non-social central attentional cues. This might suggest that endogenous orienting and gaze cueing appears to be intact in high-functioning ASD children and adolescents.

The lack of group difference in the current study might be due to the fact that older and more able individuals with ASD may learn some of the social skills which come naturally to controls, such as eye-gaze cueing and that by the time they reach childhood these differences are less apparent. Moreover, the Posner attentional cueing paradigm is an artificial experimental setting and may not be sensitive enough to detect the difficulty which individuals with ASD have in gaze-following behaviours in more naturalistic or spontaneous situations.

Across all groups, the cueing effect was observed only in response to the arrow and not gaze cue. It is, however, not clear why the social cue of a photo of a face could not elicit reflexive orienting of attention even in the control group. One explanation might be that the gaze cue was more complex than the arrow and therefore required more time to be processed.

6.10.3.11 Limitations and Suggestions for Future Research

The present study had a number of limitations. First, the sample size, although comparable to previous studies, was relatively small and unequal, and the age range was quite wide.

Furthermore, due to the time restrictions, the number of trials in each condition was kept to a minimum. A larger number of trials might ensure more reliable assessment.

Moreover, the Posner attentional cueing paradigm is an artificial experimental setting and may not be sensitive enough to detect the difficulty which individuals with ASD have in gaze-following behaviours in more naturalistic or spontaneous situations. This means that findings from these types of tasks may reflect attentional cueing, irrespective of social processing (Kingstone, 2009). It is suggested that future research focus on tasks that investigate social attention in more naturalistic settings, such as scene viewing research that is closer to the real world situations and therefore might have the potential to uncover subtle differences in gaze cueing.

6.11 Chapter Summary

In the current chapter, the Theory of Mind (ToM) and social cognition account was explored using three different experiments: the Triangle Task, Strange Stories task, and a task of social vs. non-social cueing.

Administering the Triangle Task revealed that the clinical groups performed at the same level of the control group on both goal-directed and mentalising tasks in terms of intentionality (i.e. attributing mental states to triangles) and appropriateness (i.e. understanding the intended meaning of the animation sequences). Moreover, the task could not discriminate between the clinical groups. The lack of group differentiation could be due to the high cognitive and verbal ability of the participants which could compensate for ToM incompetence.

In the Strange Stories task, all groups performed at the same level on physical stories, suggesting an intact text and sentence comprehension in the clinical groups similar to the control group. Poorer understanding of mental state stories was observed in the ADHD group compared with controls. Moreover, the two groups with ASD showed a tendency for poorer performance in stories with social content. However, the group differences appeared to be mainly due to differences in cognitive and verbal abilities.

The Cueing task found no evidence for deficits in attentional orienting to social stimuli in children and adolescents with ASD compared to controls. The two groups with ADHD showed the same pattern of response to different cue types as the ASD and control groups and across all groups, the cueing effect was observed only in response to the arrow and not the gaze cue. The lack of group difference between the ASD and control groups in the current study might be due to the fact that older and more able individuals with ASD may learn some of the social skills which come naturally to controls, such as eye-gaze cueing and that by the time they reach childhood these differences are less apparent.

In summary, none of the tasks used in this chapter could differentiate the clinical groups, suggesting that this is an area in which ADHD and ASD have cognitive overlap.

Chapter 7

Central Coherence Account

7.1 Chapter Overview

As reviewed in Chapter 1, one attempt to explain the coexistence of deficits and superior abilities in ASD is the 'Weak Central Coherence' account suggested by Frith in 1989.

In this chapter, first the relevant studies on the Weak Central Coherence (WCC) account of ASD will be addressed. Background literature on the experiments administered in the present study will then be briefly reviewed. Subsequently, the findings from each experiment will be discussed.

7.2 Central Coherence

Current cognitive accounts of ASD have focused primarily on the areas of impairment, trying to explain autism symptomatology by deficits in 'ToM' or 'EF'. However, individuals with ASD also present with an uneven profile of cognitive abilities in which outstanding talents in certain visuospatial and memory tasks are notable (Shah & Frith, 1983).

One cognitive theory that has specifically tried to address both the deficits and abilities in ASD is the WCC account.

Typically developing children and adults have a tendency to process information for meaning and gestalt (global) form, in its context, often at the expense of attention to or memory for featural information. Uta Frith introduced the term central coherence (CC) to describe this tendency and suggested that this capacity for central coherence is diminished in individuals with autism who instead show a processing bias i.e. WCC as they are attending preferentially to details, at the expense of global configuration, contextualized meaning, gist, and gestalt (Frith, 1989a).

Weak coherence has been postulated to lie at the root of characteristic autistic symptoms such as insistence on sameness, attention to parts of objects, and an uneven cognitive profile, including savant skills (Happe & Frith, 2006).

Kanner highlighted this attention to detail in his original description of autism (1943): 'inability to experience wholes without full attention to the constituent parts' and 'a situation, a performance, a sentence is not regarded as complete if it is not made up of exactly the same elements that were present at the time the child was first confronted with it' (Kanner, 1943, p. 246).

Moreover, a 'persistent preoccupation with parts of objects' is one of the current diagnostic criteria for autistic disorder (DSM-IV). This may manifest in an unusual tendency to play with specific parts of toys (e.g., spinning the wheels of a car), rather than according to its intended function (Lord, et al., 1994).

As mentioned earlier, rather than being a deficit account, WCC predicts relatively good performance where attention to detail and ignoring the context is advantageous. As WCC may facilitate certain strengths in autism, Happé (1999) proposed that the notion of a core deficit in coherence should be replaced by a *processing style*. She suggested that this tendency for local versus global processing might vary along a continuum in the normal population varying from 'strong' to 'weak' coherence. Individuals with autism are hypothesised to be at the extreme (weak) end of this distribution (Happe, 1999).

CC has been assessed in several studies which have shown that individuals with ASD show a reduced tendency to cohere information presented at basic perceptual levels in visual, auditory, and verbal domains compared to control participants. As the focus of this thesis is only on the visuo-spatial and verbal aspects, only studies related to these domains will be addressed.

7.2.1 Visuo-spatial coherence in ASD

7.2.1.1 Embedded Figures Task Performance in ASD

The Embedded Figures Task (EFT) is a visuo-spatial test which was first used to assess CC in an autistic population (Witkin, Ottman, Raskin, & Karp, 1971). In order to succeed at this test, the child must identify a simple figure, such as a triangle, embedded within a complex form. The child must disregard the whole image and what it represents and focus on the detail of the shapes and lines present in the picture.

Superior performance of individuals with ASD in the EFT has been reported in previous studies, which will be described here. In an early study by Shah and Frith (1983), individuals with autism (N=20) were assessed on the child version of EFT (CEFT). They could more accurately locate the embedded figures compared to control participants, and this was interpreted as an ability to ignore the strong gestalt of the complex form, allowing perception of local parts (Shah & Frith, 1983).

Jolliffe and Baron-Cohen, compared a group of adults with HFA (N=17) and a group of adults with Asperger's (N=17) with a group of age- and IQ-matched controls (N=17) and showed that individuals with HFA and Asperger's were faster in the EFT than controls. However, no differences in the test accuracy between the groups were reported (Jolliffe & Baron-Cohen, 1997).

van Lang et al. compared the performance of a group of adolescents with ASD who had intellectual disability (N=22) with a group of age- and IQ-matched controls (N=21) and found

that the ASD group performed better than the control group on EFT (van Lang, Bouma, Sytema, Kraijer, & Minderaa, 2006).

However, it is important to note that there are studies in children and adults which failed to show the superior performance of individuals with autism on EFT (See (Brian & Bryson, 1996; Schlooz et al., 2006)).

These inconsistent results across studies could be due to methodological issues such as different sample characteristics, i.e. cognitive ability, age range, diverse matching to control group procedures, or a range of different administration techniques and variables. For example, the studies detecting group differences in accuracy used lower-functioning groups (Ropar & Mitchell, 2001; Shah & Frith, 1983; van Lang, Bouma, et al., 2006); this could be due to the fact that these individuals had a more severe form of ASD and so differences in CC were more enhanced.

In a recent study, White and Saldana critically reviewed the previous studies on EFT in ASD (White & Saldana, 2011), stating that an issue which pervades these types of studies is how to match controls to ASD groups. Indeed, it was the studies which used younger controls, showed significant group differences in RTs (See (Jarrold, Gilchrist, & Bender, 2005; Ropar & Mitchell, 2001)).

Another issue that White and Saldana raised was the different techniques that each study used for analysing RT which could produce quite different results. For example, some authors have calculated the average RT for correct responses only (de Jonge, Kemner, & van Engeland, 2006; Morgan, Maybery, & Durkin, 2003; Pellicano, Gibson, Maybery, Durkin, & Badcock, 2005), whilst others have used the RTs for all responses (i.e., both correct and incorrect responses) (Jolliffe & Baron-Cohen, 1997; Ropar & Mitchell, 2001)(Jarrold, et al., 2005).

White and Saldana argued that since the EFT has easy and difficult items, average RTs to only correct responses may not be comparable between low and high accuracy scores. Children who have lower accuracy are likely to give correct and faster answers to the easier test items; a group with a slightly lower accuracy may therefore have a faster reaction time than participants with higher accuracy who have solved the harder items. Studies using this method may therefore artificially produce group differences. Hence, it has been suggested that the effect of accuracy should be considered when calculating the RT to the correct responses (White & Saldana, 2011).

In their own study, White and Saldana examined group and individual differences in performance on the EFT considering the different methods of analysing reaction time data within the same participants. They showed that in two large (N=45 and N=62) samples of high-functioning children (6–16 years) with ASD, the performance was similar to the controls on

accuracy and RT measures. Considering inconsistent past findings and the inability of EFT to disentangle global and local processing, they suggested that EFT should be used with caution in the future (White & Saldana, 2011).

7.2.1.2 Block Design Performance in ASD

Another visuo-spatial test which has been used to assess CC in individuals with ASD is the Block Design (BD) task in which a pattern has to be constructed from individual blocks.

Superior performance in individuals with ASD has been documented for the BD task (Happe, 1994b; Pellicano, Maybery, Durkin, & Maley, 2006; Ropar & Mitchell, 2001; Shah & Frith, 1993). Despite the high loading on nonverbal intelligence in the general population, performance in the BD subtest often has been reported to be inconsistent with general ability in individuals with ASD and peak performance in the BD, relative to other subtests has been frequently reported in the ASD literature (Happe, 1994b).

This superior performance has been explained by a specific asset for mentally segmenting the designs. This was shown in an experiment by Shah and Frith using Un/Segmented Block Design. They found that presegmenting the design to be copied helped control groups significantly more than it helped participants with ASD (Shah & Frith, 1993). They suggested that individuals with ASD readily perceived the designs in terms of their constituent parts and were not locked into the strong 'gestalt' of the design.

However, it should be noted that relatively good performance of individuals with Asperger's disorder or HFA in BD task has not been consistently found (Kaland, Mortensen, & Smith, 2007; Ozonoff, Pennington, et al., 1991; Szatmari, Tuff, Finlayson, & Bartolucci, 1990). Although there are also studies that reported higher scores on the BD task in individuals with HFA compared to controls (Caron, Mottron, Rainville, & Chouinard, 2004; Mottron, 2004), most studies have found superior performance in lower-functioning groups (Ropar & Mitchell, 2001; Shah & Frith, 1993).

The inconsistent results of the BD task across studies could be due to methodological issues such as different sample characteristics, for example, cognitive ability, age range, diagnosis and different versions of the BD task (Weschler version vs. Shah and Frith's original Un/Segmented comparisons).

In a study by de Jonge et al. (2009) which used the Un/Segmented version of the BD task, even though they did not find superior performance of individuals with ASD in terms of accuracy and RT, they did find that ASD group made significantly fewer errors during the reconstruction of the designs than control individuals. Their assumption was that individuals with superior mental segmentation abilities would place a block in the correct position within a design on the first placement; while in contrast, individuals with poorer mental segmentation skills would

more frequently place a block in an incorrect position initially and adjust it subsequently during the process of reconstruction. The authors concluded that the superiority of ASD group was best reflected in the condition that relies most on mental segmentation ability: the ability to decide exactly how and in which direction a double-coloured block must be positioned within a design (de Jonge, Kemner, Naber, & van Engeland, 2009).

7.2.1.3 Other Visuo-spatial Tasks in ASD

Individuals with ASD have been found to perform well when required to recognise objects from individual fragments, but encounter difficulties when required to integrate the fragments into a whole (Jolliffe & Baron-Cohen, 2001).

This tendency can be seen in the unusual, detail-focused drawing style which has been observed in individuals with ASD. Mottron and colleagues in a study on adolescents and adults with ASD used copying tasks to assess hierarchical aspects of visual perception. They reported a tendency in individuals with ASD to begin drawings with a local feature, rather than sketch a global outline (Mottron, Belleville, & Menard, 1999).

Booth et al. (2003) identified several markers for WCC in a simple drawing task by noting characteristics which were more apparent in ASD than in an age- and ability-matched control group. For example, boys with ASD (N=30) were more likely to begin their drawings with local features or details, draw in a piecemeal or fragmented fashion, and violate the overall configuration of the figure (Booth, et al., 2003).

Mottron et al. (2003) attempted to isolate the particular aspect of local-global processing that was deficient in ASD. They administered a battery of visual coherence tasks that tapped different processing demands: local processing, global processing or switching between the two levels, in a group of individuals with HFA (N=12, aged 9-22 years) and 12 age- and ability-matched control participants. No group differences were found in the three measures of global processing: identifying fragmented versus complete letters, identifying silhouetted versus detailed objects, and visually searching for targets identified by global grouping. Furthermore, groups did not differ in a divided attention version of the Hierarchical Figures task, in which target letters could appear at either the local or global level (although the typical global advantage was not observed in the control group on this task). Only in a measure of local processing did group differences occur. In the control group, it took longer to identify embedded versus isolated stimuli, but search times were similar for participants with HFA between the two conditions. The authors suggested that this provided evidence that ASD is associated with a local processing bias that is not necessarily a consequence of, or accompanied by, a global processing deficit (Mottron, Burack, Iarocci, Belleville, & Enns, 2003).

7.2.2 Verbal-semantic Coherence

Although focus on detail has been studied less in verbal tasks, reduced use of sentence context for disambiguation of homographs is well replicated (Frith & Snowling, 1983; Happé, 1997; Lopez & Leekam, 2003).

It has been shown that individuals with ASD have difficulties in the use of context when reading homographs presented in sentences (e.g., 'in her dress/eye there was a big tear'). Moreover, it has been shown that they are less likely to use the sentence context spontaneously to provide the context-appropriate pronunciation of a homograph, often giving the more frequent pronunciation irrespective of the contextually-determined meaning (Jolliffe & Baron-Cohen, 1999b). Jolliffe et al. suggested that individuals with ASD are impaired in achieving local coherence, and that they have a preference not to attempt coherence unless instructed to do so, or unless they make a conscious decision to do so (Jolliffe & Baron-Cohen, 1999b).

A similar disregard for sentence context has been demonstrated in the Sentence Completion Task. Booth et al. (2010) compared individuals with autism and Asperger's (N=41, aged 9–21 years, FSIQ range=49-131) to a group of age- and IQ matched controls (N=41). In their sample, the autism group was comparable in age and PIQ to those with Asperger's disorder but scored significantly lower in FISQ and VIQ. They found individuals with ASD at all levels of ability, showed a greater tendency to make local, globally inappropriate, completions to sentence stems than control participants. Moreover, they found that there was a significant correlation between IQ and the completion score in the ASD group, but not in the control group (Booth & Happe, 2010).

The lack of drive for meaning has also been shown at the narrative level. Adults with ASD were less able to arrange sentences coherently and use context to make a global inference than controls (Jolliffe & Baron-Cohen, 2000).

7.2.3 The Specificity of Weak Central Coherence in ASD

A weak drive for CC appears to be specific to individuals with ASD, although comparisons are often only made to typically developing participants. Alternative control groups have been used in a few studies, such as individuals with mental retardation (Jarrold & Russell, 1997), language disorders (Norbury & Bishop, 2002), Tourette syndrome (Ozonoff, Strayer, McMahon, & Filloux, 1994), and ADHD (Booth, et al., 2003; Booth & Happe, 2010), with a specificity of weak coherence in ASD generally confirmed.

7.2.4 Central Coherence in ASD versus ADHD

In the first direct comparison of ASD and ADHD groups, Booth et al (2003) compared boys with ASD (N=30, mean FSIQ=100) to a group of age- and IQ-matched boys with ADHD (N=30), and typically developing boys (N=31), on a drawing task requiring planning for the

inclusion of a new element. They measured weak coherence through analysis of the individual's drawing style and found that the ASD but not the ADHD participants showed detail-focused drawing styles. Their ASD individuals were more likely to begin drawing with a detail, to draw in a piecemeal fashion and to create a drawing in which configuration was violated than were the control or ADHD groups. Both the ADHD and ASD groups showed planning impairments but which were more severe in the ASD group. Moreover, they showed that poor planning did not predict detail-focused drawing styles. The authors suggested that weak coherence may indeed be a cognitive style specific to ASD and unrelated to cognitive deficits in frontal functions (Booth, et al., 2003).

In another study by Booth et al. (2010), a group of ASD individuals (N=30, mean age=11.0, and mean FSIQ=97.3) were compared to a group of age- and IQ-matched boys with ADHD (N=29), and typically developing boys on Sentence Completion and Go/No-Go tasks. They found that the ASD group produced significantly more local completions than the ADHD group. Furthermore, they showed that individuals in the ADHD group were more impulsive than the ASD group in the Go/No-Go task. They concluded that problems of inhibition do not appear, in themselves, to result in detail-focused performance in the Sentence Completion Task (Booth & Happe, 2010).

7.2.5 Age Effect

Several studies have examined the development of local-global processing. It is well documented that perceptual processing in children is fundamentally different from that in adults, and undergoes changes during development. However, there is little consensus as to the exact nature of these changes. Early developmental studies generally provided mixed results on whether 'parts or the whole' dominate children's perception.

Some studies have suggested that young children are best described as 'piecemeal' processors, attending only to the parts of a configuration (Carey & Diamond, 1977); other studies claim that young children are 'wholistic' processors, perceiving patterns as undifferentiated wholes, without awareness of constituent parts (Gibson, 1969).

Dukette and Stiles further discussed the issue and suggested that young children have an ability to attend to either the parts, to the whole pattern, or both depending on the task and stimulus conditions (Dukette & Stiles, 1996, 2001).

It has been shown that tasks which require detail-focused processing and an ability to ignore gestalt principles (e.g., EFT, BD task) also show improvement with age (Witkin, et al., 1971). An age effect has been also shown in the Sentence Completion Task with older children showing better completion performance overall (Booth & Happe, 2010).

7.2.6 Neural Substrates of Coherence

Several studies have attempted to elucidate brain regions involved in local and global processing. Neuroimaging studies using fMRI and positron emission tomography (PET) methods point towards hemispheric specialisation for global and local processing.

Fink et al. (1997) scanned healthy adults while they attended to, or switched attention between local and global levels of hierarchical figures. They showed that the areas of brain activation differed between two levels: selective attention to global features was associated with right lingual gyrus activation, while attention to local features was associated with left inferior occipital activation. The act of switching between local and global levels resulted in further activation of the anterior cingulate and the DLPFC which highlighted the role of executive attentional control in alternating attention between levels (Fink et al., 1997).

To date, there is little evidence for localised abnormalities in the brains of individuals with ASD that relate to local-global processing. Right hemisphere dysfunction in case studies of Asperger's disorder (McKelvey, Lambert, Mottron, & Shevell, 1995) and reduced white matter volume in the right hemisphere of adolescents and young adults with ASD (Waiter et al., 2005) have been reported. However, as reviewed by Bauman and Kemper (2005), many other brain regions have been implicated in ASD that are non-specific to the right hemisphere (e.g., the limbic, frontal and cerebellar regions), and it is as yet unclear which anomalies are specific or universal to ASD (Bauman & Kemper, 2005).

Ring et al. (1999) used fMRI to assess whether superior ability in the EFT in ASD was due to differences in the pattern of brain activation during task performance. They found that searching for hidden figures activated similar cerebral regions in adults with ASD and control groups, which had previously been implicated in object and visual-spatial processing, although some differences suggested that the cognitive strategies employed distinguished the two groups.

They showed that controls additionally activated prefrontal cortical areas which were not recruited in the group with ASD. Conversely, individuals with ASD showed greater activation of ventral occipitotemporal regions. This suggested that the cognitive strategies adopted by the two groups were different: the autistic group strategy depends to a large extent on early stages of sensory processing such as object feature analysis, while the control group invokes a greater contribution from high-level visual perception, such as top-down modulation (necessary to extract global features) (Ring et al., 1999).

As well as the study of particular regions of the brain, abnormalities are also suggested in brain connectivity that may underlie weak coherence in ASD. There is considerable evidence for abnormal brain connectivity in ASD from neurological studies (Belmonte et al., 2004). One explanation is that specialised brain regions that typically connect and collaborate while

performing a task, may be less connected and work in isolation in the brains of individuals with ASD. This failure to integrate information between brain regions is suggested to be indicative of WCC.

Just et al. (2004) proposed that reduced synchronisation between cortical areas, as found in their fMRI study, might explain the lack of integrative processing in ASD. They scanned their participants while responding to comprehension questions about simple sentences they read. Although both groups activated the classic language areas while performing the task, the ASD group produced more activity than the control group in Wernicke's area (left latero-superior temporal), and less activity in Broca's area (left inferior frontal gyrus). This pattern of activation in the ASD group suggested a greater degree of low-level processing (i.e., of individual words) and less high-level integration of meaning and working memory as required in sentence processing. They also reported that the degree of connectivity between cortical language regions was reduced in ASD compared to control participants (Just, Cherkassky, Keller, & Minshew, 2004).

7.2.7 The Universality of Weak Central Coherence in ASD

An issue for the validity of the WCC theory is the extent to which this processing style can be said to characterise all individuals with ASD. It has been argued that similar to the finding that impairments in ToM and executive functioning do not characterise all individuals with ASD, it is accepted that weak coherence may only be present in a proportion of those with the disorder.

The degree of universality of weak coherence in individuals with ASD has been reported in previous studies. Happé (1994b) reported that 85% (41/ 48) of her sample of children and adults with ASD were found to have peak performance on the BD task (Happe, 1994b).

In contrast, Teunisse et al. (2001) found that weak coherence was not a universal feature in their sample of high-functioning adolescents with autism as 57% (20/ 35) of their group with HFA performed below one standard deviation from the mean of the normative data on the Silhouette subtest from the Visual Object and Space Perception Test (Teunisse, Cools, van Spaendonck, Aerts, & Berger, 2001).

7.2.8 The Pervasiveness of Weak Central Coherence

ASD has been characterised by WCC in different domains: perceptual, auditory, visuo-spatial, and verbal-semantic. Some studies have examined whether this processing style shows consistent individual differences *across* levels and domains. Fundamentally, performance on all coherence tasks should correlate if the same construct is being measured.

The consistency of CC within the same processing domain has mainly been studied in the visuo-spatial domain. This may be because experimental support for weak coherence in the ASD literature is more robust in this domain compared to the auditory/verbal modality.

Ropar and Mitchell (2001) compared performance across three visuo-spatial tasks: the EFT, the Wechsler Block Design subtest, and the Rey Complex Figure (accuracy in copy and immediate recall). The task battery was administered to children with autism (N=19, aged 9-18 years), Asperger's disorder (N=11, aged 8-15 years), moderate learning difficulties (MLD) (N=20, aged 9-14 years), and two groups of typically developing children, aged 8 years (N=19) and 11 years (N=18). They reported strong correlations in all groups between the three measures, which generally remained after the effects of age and verbal mental age (VMA), were controlled for (with the exception of the MLD group and the youngest TD group) (Ropar & Mitchell, 2001).

Jolliffe and Baron-Cohen (1999) explored coherence in the verbal domain. High-functioning adults with autism or Asperger's disorder showed impairment in the use of sentence context to determine the correct pronunciation of homographs or to interpret an ambiguous sentence read out to them. They also had difficulty with inferential reasoning when required to select the most appropriate bridging sentence. The three verbal coherence tasks were found to correlate with each other suggesting that a unitary force may have driven performance, possibly WCC (Jolliffe & Baron-Cohen, 1999b).

7.3 Summary

A weak drive for central coherence has been reported in individuals with ASD compared to controls across several domains: perceptual, auditory, visuo-spatial, and verbal-semantic. This appears to be specific to individuals with ASD, although comparisons are often only made to typically developing participants. Alternative control groups such as individuals with mental retardation, language disorders, Tourette syndrome, and ADHD, have been used in a few studies, with the specificity of weak coherence to ASD generally confirmed.

However, it is important to note that there are studies that failed to show the tendency for WCC in individuals with ASD and findings are inconsistent across studies using similar measures.

An issue for the validity of WCC theory is whether this processing style can be said to characterise all individuals with ASD or if it is only present in a proportion of those with the disorder. Another issue is the pervasiveness of WCC across different domains, i.e., whether this processing style shows consistent individual differences across levels and domains and originates from one central driving force or whether these are independent processes.

Assessment of local/global processing across processing levels/modalities would help to address Frith's original conceptualisation of weak coherence, as a 'central force' to perceive and understand the world, pervasive in all levels of processing in individuals with ASD.

7.4 Aims

This part of the study aims to replicate and extend previous findings from studies on childhood neurodevelopmental disorders. It will help to determine: (1) whether the present sample confirms the WCC account in ASD, (2) whether weak coherence is specific to ASD and whether individuals with ASD can be distinguished from individuals with ADHD on the basis of their performance in the tasks assessing CC, (3) the impact of comorbidity by comparing the performance of the comorbid group with pure clinical groups, and finally, (4) the effect of brain development on task performance.

7.5 Central Coherence Measures

Three established tests of CC were used for the purpose of this PhD study: (i) the Embedded Figures Task and (ii) the Block Design task, both in the visuo-spatial domain and (iii) the Sentence Completion Task, in the verbal-semantic domain.

The tasks will be presented in three separate sections (Experiment 1, 2 and 3), with a summary of the key findings.

7.5.1 Experiment 1: Embedded Figures Task

The Embedded Figures Task (EFT) (Witkin, et al., 1971) is a commonly used perceptual test of cognitive style. The task involves locating a simple shape within a larger complex figure that has been designed to obscure or embed the simple shape. In the children's version of the task (CEFT) (Karp & Konstadt, 1963), the complex figure is a meaningful picture, while in the standard EFT, the complex figure consists of a non-meaningful geometric design. Successful performance is dependent on the ability to resist the tendency to see only the global form or be drawn in by the surrounding context.

High accuracy and high speed are considered as an index for weak coherence, as it suggests that participants focus more on the elementary constituents of which the complex designs are composed (Loth, Gomez, & Happe, 2008).

7.5.1.1 Method

A modified version of the EFT was used, including seven items from the CEFT (all 'house' shaped items: 3, 4, 6, 9, 11, 12, and 14) and eight items from the standard version (items: 1, 4, 5, 6, 8, 10, 11, and 12). Selected items ranged in difficulty in order to produce variability between participants and avoid ceiling effects across the age levels tested. Test items were presented on laminated cards and each simple form was given to the participant on a transparent sheet. See Figure 7-1 for two examples from the standard EFT.

7.5.1.2 Procedure

Participants were first shown a simple shape and told they would soon see a picture that had this shape hidden within it. They were informed that the hidden shape would be the same size and orientation as the simple shape and they had to find it as quickly as possible. The simple shape remained in view while the test item was presented.

The first stimulus of each child and standard set was for practice in order to make participants aware of the task requirements. During the practice, children were encouraged to place the cut-out target shapes on top of the hidden shapes in order to leave no ambiguity in task understanding. During the test trial, the experimenter asked the participant to first point to the target shape and to show the outline and then place the cut-out form over his chosen location.

Timing began as soon as the picture (i.e. the complex figure) was revealed to the participants and stopped when the participants had indicated they had found the simple shape (by pointing or announcing). Participants were asked to demonstrate the position of the simple shape by placing the transparent sheet over the complex picture.

If they were incorrect, the simple shape was returned to its position and the participant was encouraged to search again and timing was resumed. A maximum of 60s was allowed for each picture. If they were unable to locate the shape within this time, the item was recorded as a failure.

Variable measures were the number of correct solutions (accuracy), time taken to find shape (reaction time (RT)) in seconds, and the number of false claims before finding the shape. Following the study by White and Saldana (White & Saldana, 2011), RT was calculated in three ways: firstly RT to correct trials only, secondly RT with 61s entered for incorrect trials, and lastly RT to correct trials with accuracy scores covaried out of them.

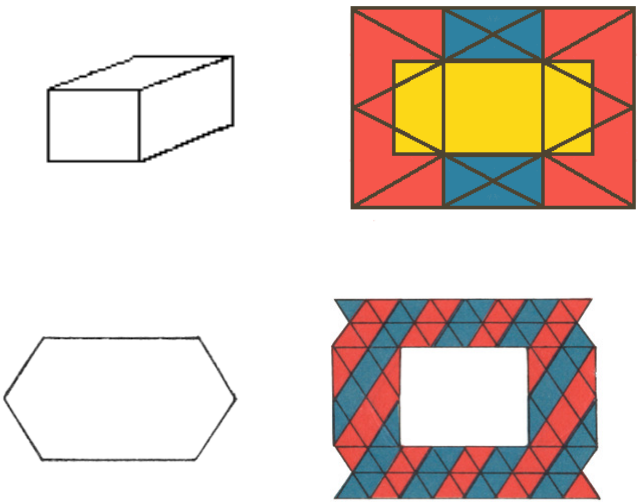


Figure 7-1: Two examples of standard Embedded Figures Task stimuli (complex picture on the right and the corresponding simple shape on the left)

7.5.1.3 Hypotheses

Fast and accurate performance in the EFT is predicted to be a key indicator of WCC. Superior performance in the EFT has previously been demonstrated in ASD. It was predicted that the ASD group would outperform the control group in the present study.

Given the poor attention in the ADHD group, poor performance (i.e. less accurate) was predicted in the EFT in individuals with ADHD compared with controls and the ASD group.

No study has evaluated EFT performance in individuals with a diagnosis of comorbid ASD and ADHD. Therefore, exploratory analyses were conducted to explore whether individuals with a comorbid diagnosis performed in a similar way to the ASD or ADHD group.

7.5.1.4 Results from Embedded Figures Task

Data were available from 115 individuals including 19 ASD, 35 ADHD, 42 comorbid, and 19 controls.

Table 7-1 presents demographic information by group for participants who completed the EFT.

No significant differences in age among the groups ($p>.05$) were observed. However, significant differences were found for FSIQ, PIQ, and VIQ (all $p<.05$). Further analysis showed that the two groups of children with ADHD symptomatology (pure ADHD and comorbid groups) had significantly lower FSIQ, PIQ, and VIQ compared to controls (LSD post-hoc tests, all $p<.05$), whereas the ASD group did not differ from controls (all $p>.05$). Also, the ASD group had a significantly higher FSIQ relative to the ADHD group ($p<.05$). However, no significant differences amongst the clinical groups were observed for PIQ and VIQ (all $p>.05$).

Table 7-1: Group descriptive for participants who completed the EFT: Means (SD), [Range]

	ASD (N=19)	ADHD (N=35)	Comorbid (N=42)	Controls (N=19)	$F_{(3,111)}$	P	Post-hoc LSD
Age in months [Range]	133.42 (19.70) [96-168]	132.26 (31.89) [84-191]	127.58 (25.51) [87-200]	126.63 (29.58) [91-180]	.38	.77	
FSIQ [Range]	111.47 (15.98) [77-139]	100.69 (14.16) [70-135]	105.64 (13.14) [79-142]	122.63 (13.20) [104-149]	10.95	<.001	Controls> ADHD, Comorbid* ASD>ADHD*
PIQ [Range]	108.05 (14.54) [80-136]	99.00 (13.85) [64-131]	104.19 (13.22) [75-141]	115.79 (12.89) [100-141]	6.64	<.001	Controls> ADHD, Comorbid*
VIQ [Range]	112.47 (18.47) [78-145]	102.34 (15.89) [75-133]	105.79 (14.57) [77-146]	124.26 (13.91) [102-151]	9.13	<.001	Controls> ADHD, Comorbid*

**Post-hoc test, p<.05,*

7.5.1.4.1 Group Comparisons in the Embedded Figures Task

Initial analyses were conducted without adjusting for age and IQ. Group differences were explored using ANOVA with group as the between-subjects factor. Accuracy was excessively skewed and none of the transformations could normalize it, therefore it was age standardised. The new accuracy variable was normally distributed and was used in the analysis.

Table 7-2 shows descriptive statistics (mean, standard deviation) in the EFT for child and standard versions separately and Table 7-3 shows descriptive statistics in EFT after combining the scores from the child and standard versions. The effect sizes were calculated for pairwise comparisons (Table 7-4). As the pattern of findings were similar when the data on the child and standard version were analysed separately and combined, only the results from the combined scores will be discussed. Moreover, only the combined scores were used in the correlational analyses.

All groups seemed to be performing at the same level of accuracy ($F_{(3,111)}$=.43, p=.73, η^2=0.012) as all groups correctly found the embedded figure in bout 90% - 92% of test trials.

For the first method where RTs were calculated only for correct responses, surprisingly the two groups with ADHD were non-significantly quicker than the ASD and control groups ($F_{(3,111)}$=1.42, p=.24, η^2=0.037). As shown in Table 7-4, medium effect sizes of the difference were observed between the control and ADHD groups (d=.49) and also between control and comorbid group (d=.48); however, the power of these analyses was limited for a .05 two-sided level of significance (power=.44, power=.42, respectively).

When the second method was applied and RT was calculated for all trials, again no significant differences were observed between the groups ($F_{(3,111)}$=.74, p=.53, η^2=0.020). Again, the two groups with ADHD were quicker than the ASD and control groups with medium effect sizes of the difference being observed between control and ADHD groups (d=.44) and also between ASD and ADHD groups (d=.32); however, the power of these analyses was limited for a .05 two-sided level of significance (power=.32, power=.19, respectively).

In an attempt to reduce the influence of different accuracy rates on reaction times, an ANCOVA was performed on the mean reaction time for correct responses, with accuracy entered as a covariate (Table 7-3). Again, no significant group differences were found with this method ($F_{(3,110)}$=1.48, p=.22, η^2=0.039)(Figure 7-2).

The only significant group difference was found in the number of false claims ($F_{(3,111)}$=4.06, p=.009, η^2=0.099) as the two groups with ADHD (i.e. ADHD and comorbid groups) showed a significantly higher number of false claims than the ASD group with large effect sizes (with the post-hoc LSD, p=.04 for ADHD-ASD comparison and p=.02 for comorbid-ASD comparison). No difference was observed between ASD and control groups (p>.05). Medium effect sizes of

the difference were observed between control and ADHD groups (*d*=.48) and also between control and comorbid groups (*d*=.59); however, the power of these analyses was limited for a .05 two-sided level of significance (power=.42, power=.59, respectively).

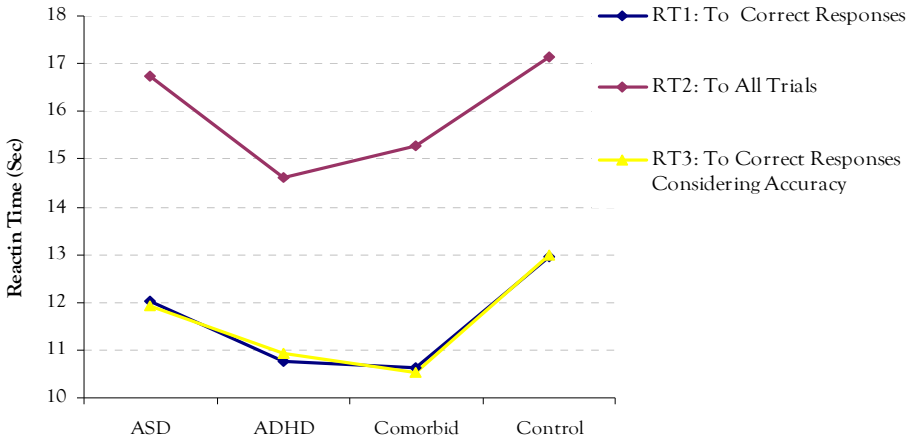


Figure 7-2: Reaction Times based on different methods of calculation

Table 7-2: Group comparisons on EFT: Child and standard versions: Means (SD)

	ASD (N=19)	ADHD (N=35)	Comorbid (N=42)	Control (N=19)	Group effect		Post-hoc LSD
					$F_{(3,111)}$	P	
CEFT Accuracy (%)	87.22 (17.75)	91.43 (11.07)	89.12 (13.31)	90.98 (8.53)	.53	.66	
CEFT RT1: to Correct Responses (Sec)	13.25 (7.31)	11.58 (5.96)	11.57 (6.35)	13.04 (5.99)	.52	.67	
CEFT RT2: to All Trials (Sec)	19.52 (10.30)	15.55 (8.06)	16.58 (9.91)	17.06 (6.64)	.82	.48	
CEFT False Claims	2.11 (2.13)	4.74 (4.54)	3.83 (3.32)	2.68 (2.94)	2.83	.04	ADHD>Control, ASD*
EFT Accuracy (%)	92.11 (13.31)	92.86 (10.63)	90.18 (13.11)	90.79 (10.90)	.35	.79	
EFT RT1: to Correct Responses (Sec)	10.60 (6.11)	9.96 (5.16)	9.83 (5.59)	12.92 (5.79)	1.50	.22	
EFT RT2: to All Trials (Sec)	14.32 (7.99)	13.79 (6.26)	14.13 (8.63)	17.15 (8.45)	.85	.47	
EFT False Claims	3.21 (2.68)	4.66 (3.50)	5.95 (4.32)	4.05 (2.76)	2.94	.04	Comorbid>Control, ASD*

CEFT=Child version of EFT; RT=Reaction Time

** Pos-hoc test, p<.05*

Table 7-3: Group comparisons on Embedded Figures Task: Means (SD)

	ASD (N=19)	ADHD (N=35)	Comorbid (N=42)	Control (N=19)	Group effect		Post-hoc LSD
					$F_{(3,111)}$	P	
Accuracy (%)	89.82(11.19)	92.19(7.32)	89.68(11.61)	90.88(7.44)	.43	.73	
RT1: to Correct Responses (Sec)	12.02(5.46)	10.77(3.77)	10.62(4.70)	12.97(5.06)	1.42	.24	
RT2: to All Trials (Sec)	16.75(7.81)	14.61(5.07)	15.27(8.06)	17.13(6.41)	.74	.53	
RT3: to Correct Responses accounting for Accuracy (Sec)	11.94(4.49)	10.92(4.73)	10.52(4.54)	12.99(4.49)	1.48	.22	
False Claims	5.32(2.93)	9.40(6.26)	9.79(5.61)	6.74(4.74)	4.06	.009	Comorbid,ADHD>ASD,Control*

**Pos-hoc test, p<.05*

Table 7-4: Effect sizes (d) of the Embedded Figures Task

	Control-ASD	Control-ADHD	Control-Comorbid	ASD-ADHD	ASD-Comorbid	Comorbid-ADHD
Accuracy (%)	.11	-.18	.12	-.25	.01	-.26
RT1: to Correct Responses(Sec)	.18	.49	.48	.27	.27	-.03
RT2: to All Trials (Sec)	.05	.44	.25	.32	.19	.10
False Claims	.36	-.48	-.59	-.83	-1.00	.06

The effect of age and IQ was evaluated using an ANCOVA on task variables with group as the between-subjects variable and age and FSIQ as covariates. When adjusted for age, the findings did not substantially differ from the analysis unadjusted for age and the group differences on false claims remained significant ($F_{(3,110)}$=4.39, p=.006, η^2=0.107). However, using FSIQ as a covariate attenuated the findings and this time the group differences on false claims showed only a non-significant trend ($F_{(3,110)}$=2.38, p=.07, η^2=0.061). Further analysis was carried out entering age and FSIQ as covariates. This time, the group difference was no longer significant ($F_{(3,109)}$=1.93, p=.13, η^2=0.050).

7.5.1.4.2 Effects of Age and IQ

Table 7-5 shows the correlation between the EFT variables, age and FSIQ across all participants. Overall, across the groups, the number of false claims was moderately correlated with age (r=-.35, p<.001) and FSIQ (r=-.34, p<.001), indicating a lower number of false claims in older participants and individuals with higher cognitive ability. There was a mild to moderate correlation between RT and age (RT1 and age: r=-.29, p=.001; RT2 and age: r=-.38, p<.001), indicating a faster response in older participants. Moreover, accuracy was moderately correlated with age (r_s=.27, p=.002) and FSIQ (r_s=.25, p=.004), indicating better performance in EFT in older participants and individuals with higher cognitive ability.

Table 7-6 shows the correlation between the EFT variables, age and FSIQ, for each group. The effect of age on accuracy was significantly greater in the ASD group than controls (z=2.32, p=.02).

No differences in the magnitude of the correlation coefficients between age and other task variables or FSIQ and EFT variables were observed between groups (Fisher's r-to-z transformation, p>.05).

Table 7-5: Correlation between EFT measures, age and FSIQ across all Groups

	Accuracy (%)	False Claims	RT 1: to Correct Trials	RT 2: to All Trials (Sec)
Age	.27**	-.35**	-.29**	-.38**
FSIQ	.25**	-.34**	.18*	-.01

** Correlation is significant at the 0.05 level.* *** Correlation is significant at the 0.01 level*

Table 7-6: Correlation between EFT measures, age and FSIQ for each Group

	Age* Accuracy	FSIQ* Accuracy	Age* False Claims	FSIQ* False Claims	Age* RT1+	FSIQ* RT1	Age* RT2++	FSIQ* RT2
ASD	.57**	.45*	-.25	-.04	-.46*	.27	-.73**	-.01
ADHD	.38*	.34*	-.50**	-.28	-.29*	.09	-.48**	-.15
Comorbid	.22	.19	-.13	-.41**	-.41**	.06	-.41**	-.03
Control	-.17	.51*	-.58**	-.22	-.02	.01	-.03	-.25

+ RT1: Reaction Time to Correct Trials (Sec), ++ RT2: Reaction Time to All Trials (Sec)

** Correlation is significant at the 0.05 level,* *** Correlation is significant at the 0.01 level.*

7.5.1.4.3 Correlation between Task Measures

Across all groups, RT to correct trials was highly correlated with RT to all trials (r=.77, p<.001). Accuracy was significantly correlated with RT to all trials (r=-.67, p<.001), indicating that individuals who quickly found the embedded figure were also more accurate. No significant correlation was observed between accuracy and the number of false claims (p>.05). The pattern of correlation, when conducted further within each group, was identical to the whole group findings.

7.5.1.4.4 Correlations between Task Measures and Clinical Measures

Correlations between EFT measures and clinical measures including Conners score, SCQ and selective scores of SDQ (SDQ total score and SDQ hyperactivity) were assessed across the groups (see Table 7-7). Analysis of correlation was then conducted within each group (see Table 7-8).

Table 7-7: Correlation between EFT measures and clinical measures across all groups

	Conners Inattention	**Conners Hyperactivity /Impulsivity**	**SCQ**	**SDQ Total**	**SDQ Hyperactivity**
Accuracy (%)	.04	-.20*	-.04	.06	-.19*
False Claim	.32**	.21*	.08	.05	.15
RT to Correct Responses (Sec)	-.21*	-.32**	-.23**	-.34**	-.25*

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level*

In the control group, a significant correlation was observed for false claims with SDQ total score (r=.66, p=.01) and SDQ hyperactivity subscale (r=.73, p=.006). The correlations remained significant after covarying for age and FSIQ. Moreover, significant correlations were observed between accuracy and Conners hyperactivity/impulsivity (r_s=.40, p=.04) and Conners inattention (r_s=.59, p=.004), suggesting more accurate responses in those with more traits of hyperactivity/impulsivity and inattention.

In the ASD group, there was a significant correlation between RT to correct responses and SCQ Score (r=-.39, p=.04), suggesting slower responses in those with more autistic symptoms. However, when age was controlled for, the correlation was no longer significant. Moreover, there was a significant correlation between false claims and Conners inattention (r_s=.41, p=.04).

The ADHD group showed only a modest correlation between false claims and PACS hyperactivity (r=.37, p=.01). Moreover, there was a modest correlation between PACS hyperactivity and RT to correct responses (r=-.31, p=.03) indicating faster responses and higher

rate of false claims in those with higher hyperactivity scores. The correlations remained significant after controlling for the effects of age and FSIQ.

Finally, in the comorbid group the relationship between EFT measures and autistic symptoms as well as ADHD symptoms was assessed. A significant correlation was observed between the RT to correct responses and Conners hyperactivity/impulsivity (r_s=-.38, p=.006), reflecting faster responses in individuals with more symptoms of hyperactivity and impulsivity.

Table 7-8: Correlation between EFT measures and clinical measures for each group (Unadjusted for age and FSIQ)

	Accuracy (%)	False Claims	RT to Correct Responses (Sec)
Controls			
Conners Inattention	.40*	.23	-.45*
Conners Hyperactivity /Impulsivity	.59**	.13	-.03
SCQ	.30	.29	.22
SDQ Total	-.07	.66*	-.31
SDQ Hyperactivity	.32	.73**	-.21
ASD			
Conners Inattention	.24	.41*	-.23
Conners Hyperactivity/ Impulsivity	.21	.08	-.32
SCQ	-.06	-.24	-.39*
SDQ Total	.44	-.16	-.36
SDQ Hyperactivity	.19	-.20	-.03
ADHD			
Conners Inattention	.01	.18	.21
Conners Hyperactivity/ Impulsivity	.19	.08	-.16
SCQ	.12	.04	-.28
SDQ Total	-.26	-.15	-.30
SDQ Hyperactivity	-.06	-.25	.09
Comorbid			
Conners Inattention	-.17	.15	-.26
Conners Hyperactivity/ Impulsivity	.12	-.05	-.38**
SCQ	.17	-.009	-.23
SDQ Total	.09	-.07	-.09
SDQ Hyperactivity	.22	.05	-.15

**Correlation is significant at the 0.05 level,* ***Correlation is significant at the 0.01 level*

7.5.1.5 Discussion of the Embedded Figures Task

The specificity of weak coherence to ASD has been generally confirmed in previous studies, although comparisons are often only made to typically developing participants. This is the first study comparing the performance of ASD individuals in the Embedded Figures Task with individuals to ADHD and comorbid group.

Superior performance of individuals with ASD in EFT has been found in the previous studies (Jolliffe & Baron-Cohen, 1997; Ropar & Mitchell, 2001; Shah & Frith, 1983; van Lang, Bouma, et al., 2006); however contrary finding have also been reported where this superior performance in children and adults with ASD was not confirmed (Brian & Bryson, 1996; Kaland, et al., 2007; Schlooz, et al., 2006; White & Saldana, 2011).

In the present sample, no group differences were found in the measures traditionally used in research involving the EFT: accuracy scores, RT for correct items or RT for all items. Individuals with ASD did not show superiority in terms of accuracy and speed in the task performance in comparison to the control group as was expected. A corrected RT measure which takes different accuracy scores into consideration was also calculated in line with the study by White and Saldana (White & Saldana, 2011). No group differences were observed in the current study for the RT to correct responses whilst accounting for accuracy, which supported the findings by White and Saldana.

The only significant group difference observed was in the number of false claims which was higher in the two groups with ADHD than ASD and control groups and showed an association with hyperactivity/impulsivity symptoms. However, it appeared that the difference in false claims could be mainly due to the lower cognitive ability of individuals with ADHD and the comorbid group as the difference disappeared after controlling for FSIQ.

The correlation between the task performance and clinical measures revealed that across the groups, symptoms of inattention and hyperactivity were related to higher rates of false claims, lower accuracy and faster responses. Moreover, autistic behaviours were associated with faster responses in finding the embedded figures.

In the control group, it was observed that the individuals with more traits of inattention and hyperactivity/impulsivity were more accurate in finding the embedded shape which was against the expectations. It seemed as if inattentiveness and impulsiveness were advantageous in that those who were less focused and more impulsive could search more areas for the hidden shape and therefore, were more accurate.

It should be noted that the two groups with ADHD were faster in finding the embedded figures than ASD and controls, even though the difference did not reach significance. In these two ADHD groups, this quicker pattern of responding was related to hyperactivity/impulsivity

symptoms and can be explained by the attitude of individuals with ADHD. They might have been more impulsive and willing to go with their initial perception; they were also less cautious as they showed higher false claims compared with the other two groups. Being more impulsive and having more claims therefore was advantageous as they could find the embedded figures faster. This attitude did not adversely affect their performance as they showed the same level of accuracy as the ASD and control groups.

In the ASD group, autistic behaviours were found to be associated with faster responses in finding the embedded figures; however, the association did not survive after controlling for age.

EFT performance has been predicted to improve with age and intellectual ability in children (Witkin, et al., 1971). This has been confirmed in the present study as there was an association between age and cognitive ability with the task performance.

As mentioned earlier, the inconsistent results of EFT across studies could be due to methodological issues such as different sample characteristics (i.e. cognitive ability, age range, diagnosis, diverse matching to control group procedures, and a range of different administration techniques and variables).

Studies that have included participants at the high ability end of the spectrum (as in the present study) have not reliably found the predicted result of superior performance in individuals with ASD in EFT (Kaland, et al., 2007; Ropar & Mitchell, 2001; White & Saldana, 2011), whereas the studies detecting group differences in accuracy used lower-functioning groups (Ropar & Mitchell, 2001; Shah & Frith, 1983; van Lang, Bouma, et al., 2006). This raises the question as to whether WCC, at least at a visuo-spatial level, is less characteristic for relatively able individuals with Asperger's or HFA, as compared with less able individuals with autism, and therefore whether this processing style may be more prevalent in low-functioning individuals or not.

Another issue that pervades the literature on ASD is how to match control groups to ASD groups. The present study chose age-matched controls; however, the studies by Jarrold et al. (Jarrold, et al., 2005) and by Ropar and Mitchell (Ropar & Mitchell, 2001), which both showed significant group differences in reaction times, used younger children as controls. It is perhaps unsurprising that the older children with ASD performed better than the younger control children.

As White and Saldana suggested, the different techniques of analysing reaction time in different studies could produce quite different results and make the interpretation of findings difficult. Some authors have calculated the average RT for correct responses only (de Jonge, et al., 2006; Morgan, et al., 2003; Pellicano, et al., 2005), whilst others have used the RT to all stimuli (Jarrold, Gilchrist, & Bender, 2005; Jolliffe & Baron-Cohen, 1997; Ropar & Mitchell, 2001). In the current study, RT was calculated in three different ways in order to reduce the effect of

different techniques of analysing RT may have on the findings. However, even though the third method is a more accurate way of calculating the RT, in the present sample it did not differ from the RT to correct trials and therefore, it did not change the results. This can be explained by the fact that all groups performed the EFT at the same level of accuracy.

Another reason why findings of the present sample may not support previous studies could be that only a proportion of the ASD population actually has WCC (Happe & Booth, 2008). Therefore, it is possible that a different sample of the ASD population would by chance contain more children with performance outside the control range, producing a stronger group difference, especially if the sample was small.

One of the strengths of the present sample was considering the effect of comorbid ADHD in individuals with ASD which has been neglected in previous studies. As explained, the pattern of performance in the comorbid group was to a large extent similar to the ADHD group; that is, the superior performance of individuals with ASD (i.e. the faster RT) reported in previous studies could be to some extent due to the unmeasured comorbid ADHD.

7.5.1.6 Conclusion

The current study extends previous research by comparing the ASD group with a group of age and IQ-matched controls. It is the first to compare the performance of ASD with those with ADHD on EFT and taken into account the co-occurrence of the symptoms of ADHD and ASD when comparing the two groups.

The weaker drive for central coherence in individuals with ASD has not been confirmed which could be due to different sample characteristics and methodological issues.

An interesting finding in the present sample is that the pattern of performance in the comorbid group was to a large extent similar to the ADHD group which in turn would suggest that the quicker RT in the autism group on EFT, reported in previous studies could be to some extent due to the unmeasured comorbid ADHD.

Looking at the performance of individuals with ADHD on EFT (i.e. the high number of false claims though at the same time performing fast and accurate), would indicate that the scoring system of EFT needs some revisions. It seems that the current scoring criteria even promote the performance of impulsive individuals who do not consider being cautious and accurate on the task and gives them credit of a better performance as they can even randomly locate the embedded figure after several guess. It is therefore suggested that other criteria such as a limit for the number of false claims should be added to the scoring system.

The fact that the ADHD group outperformed the ASD group in RT and showed the same level of accuracy, queries the validity of the EFT as a task measuring the detail-focused style of individuals with ASD and further suggests that the EFT should be revisited in future studies.

7.5.1.7 Limitations and Suggestions for Future Research

The present study has a number of limitations. First, the sample size, although comparable to previous studies, was relatively small and unequal, and the participants' age range was quite wide.

It is suggested that future research reassess the WCC style and its specificity in ASD by comparing the performance of individuals with ASD on EFT in comparison to alternative control groups such as ADHD using a larger sample. It is also recommended that they consider the co-occurrence of ADHD in their ASD group in order to control for its confounding effect.

7.5.2 Experiment 2: Block Design Task

The Block Design test was originally developed by Kohs (1923) (Kohs, 1923) as a measure of general intelligence. Since its inception, it has become a well-established subtest of the Wechsler scales (Wechsler, 1992). A detail-focused processing style is predicted to be advantageous to the ability to analyse a design in its constituent parts.

High accuracy and speed in this task are considered as an index for weak coherence because participants seem to be less affected by the design's configural gestalt (Shah & Frith, 1993).

7.5.2.1 Method

The Block Design subtest of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1997) was used. The task requires the participant to reconstruct designs using red and white coloured blocks. The materials consist of nine identical red and white blocks and 13 designs in total. Each block has two red sides, two white sides and two sides that are half red and half white with the division oriented along the diagonal. The target-designs are printed in red and white and presented in a booklet. The 13 designs progress in difficulty from a simple design requiring only two blocks (the first design: 1 by 2 squares) to more complex designs requiring four blocks (including 8 designs: 2 by 2 squares), and finally to ones which need all nine blocks to be constructed (the final four designs: 3 by 3 squares).

7.5.2.2 Procedure

The standardised instructions from the WASI manual were adhered to with differing starting points depending on the participant's age. For participants aged 6 to 8 years, design 1 was administered first, and for those 9 years and older, design 3 was the starting point. Participants were first familiarised with the two-coloured blocks and shown how the blocks were identical with different coloured sides.

The participant was instructed to construct the designs shown by the experimenter and was encouraged to do so as quickly as possible. First, a practice item was administered in order to make the participant aware of the task requirements, with the experimenter first demonstrating

the design using the blocks and then placing it in front of the participant, asking him to replicate it. A rotation error was also demonstrated (i.e., the blocks rotated more than 30 degrees from the horizontal) and the participant was informed this answer would be incorrect. The blocks were scrambled and the participant was asked to assemble the blocks to match the practice item. The experimenter repeated the demonstration if the participant arranged the blocks incorrectly, and the participant was given the opportunity for a second attempt.

After the participant successfully constructed a practice item (either two-block or four-block), the subsequent designs were administered in a fixed order. Once the participant indicated he had completed a design, the blocks were scrambled and the next design was presented. There was a stopping rule: if the participant failed to reconstruct three subsequent designs, the test was discontinued.

Designs 1 to 4 consist of two trials, and designs 5 to 13 consist of only one trial. Based on the manual, for designs 1 to 4, the second trial was administered if the participant failed to construct the design. Participants were given 60s maximum to construct the 2-block and 4-block designs and 180s for the 9-block designs.

The experimenter recorded the accuracy of each construction and the time to complete in seconds. Timing began as soon as the design in the booklet was revealed to the participants and stopped when the participants had indicated they had completed the construction.

Each design was scored and a composite ability score (the raw score) was calculated according to the WASI manual. The composite ability score takes into account the time spent by each individual to construct each design. Finally, based on the WASI manual, the raw score was converted to a BD T-Score based on the individual's age range. Therefore, the variable measures for the BD task were the number of correct solutions, the BD raw score, and the BD T-Score.

7.5.2.3 Hypotheses

The ASD literature suggests that proficient Block Design performance is a marker of weak coherence due to an enhanced ability to break down the design into its constituent parts (Shah & Frith, 1993). It was predicted that the ASD group would outperform the control and ADHD groups in the present study.

Individuals with ADHD were predicted to perform poorer than the other group due to their general attentional problems which might adversely affect the task performance.

No prediction was considered in the comorbid group and exploratory analyses were carried out to discover their performance level.

7.5.2.4 Results from the Block Design Subset

Data were available from the whole sample: 120 individuals including 19 ASD, 35 ADHD, 42 comorbid, and 24 controls. Sample characteristics for the Block Design task are therefore the same as presented in Table 4-3 in Chapter 4.

7.5.2.4.1 Group Comparisons in the Block Design Subset

Initially, analyses were conducted without adjusting for age and IQ. Group differences were explored using ANOVA with group as the between-subjects factor (see Table 7-9). The effect sizes were calculated for pairwise comparisons (Table 7-10).

Individuals in the control group could construct more designs compared to the clinical groups; however, no group differences were observed in the number of correctly constructed designs ($F_{(3,116)}$=1.59, p=.19, η^2=0.039). Medium effect sizes of the difference were observed between ADHD and controls (d=.53); however, the power of this analyses was limited for a .05 two-sided level of significance (power=.52).

Also, no significant group differences were observed for the BD raw score ($F_{(3,116)}$=1.88, p=.13, η^2=0.046), even though the raw score was lower in the two groups with ADHD. A large effect size of the difference was detected between ADHD and control groups (d=.60), and a medium effect was detected between ADHD and ASD groups (d=.47); however, the power of these analyses was limited for a .05 two-sided level of significance (power=.55 and power=.33, respectively).

The only significant difference was found for the BD T-score ($F_{(3,116)}$=4.66, p=.004, η^2=0.108) where the individuals with pure ADHD showed a lower T-score compared to the other groups (post-hoc LSD, p=.04 for ADHD-ASD, p=.03 for ADHD-comorbid, and p<.001 for ADHD-control comparisons).

The effect of age and IQ was evaluated using an ANCOVA with group as the between-subjects variable and age and VIQ as covariates. As Block Design is a measure of PIQ and PIQ is a construct of FSIQ; in order to control for the effect of IQ, VIQ was entered as a covariate.

When adjusted for age, the findings differ substantially from the analysis unadjusted for age. This time, the number of correctly constructed designs showed significant group differences ($F_{(3,115)}$=3.12, p=.02, η^2=0.075) with post-hoc analysis showing that the control group had a significantly higher number of correct designs than the ADHD group (post-hoc LSD, p=.003). Moreover, significant group differences were observed this time for the BD raw score ($F_{(3,115)}$=3.93, p=.01, η^2=0.093) with the ADHD group scoring significantly lower than the other three groups (post-hoc LSD, p=.03 for ADHD-ASD, p=.05 for ADHD-comorbid, and p=.001 for ADHD-control comparisons).

However, when adjusted for VIQ, no significant group differences were observed for any of the task measures: the number of correctly constructed designs ($F_{(3,115)}$=.66, p=.58, η^2=0.017), the BD raw score ($F_{(3,115)}$=1.03, p=.38, η^2=0.026), and the BD T-score ($F_{(3,115)}$=1.76, p=.16, η^2=0.044).

Further, with age and VIQ entered as covariates, the findings did not change from when only VIQ was controlled for (in order not to be repetitive, the statistics were not reported).

Table 7-9: Group comparisons on Block Design Task: Means (SD)

	ASD (N=19)	ADHD (N=35)	Comorbid (N=42)	Control (N=24)	Group effect		Post-hoc LSD
					$F_{(3,116)}$	P	
Number of Correct Designs	8.74 (3.00)	7.66(2.97)	8.17(2.66)	9.21(2.86)	1.59	.19	
BD Raw Score	31.42(17.09)	23.80(15.34)	27.45(13.68)	32.08(14.40)	1.88	.13	
BD T-Score	54.79(10.49)	49.26(9.65)	54.25(9.50)	58.63(9.32)	4.66	.004	ASD, Comorbid, Control >ADHD*

**Post-hoc test, p<.05*

Table 7-10: Effect sizes (d) of the Block Design Task

	Control-ASD	Control-ADHD	Control-Comorbid	ASD-ADHD	ASD-Comorbid	Comorbid-ADHD
Number of Correct Designs	.16	.53	.38	.36	.20	.18
BD Raw Score	.04	.60	.33	.47	.26	.25
BD T-Score	.39	.99	.46	.55	.05	.52

7.5.2.4.2 Effects of Age and IQ

As the Block Design subset is a part of WASI and was designed as a measure of general intelligence, the correlation was run between the task measures and VIQ instead of FSIQ.

Overall, across the groups, age was significantly correlated with the number of correctly constructed designs (r=.55, p<.001) and the BD raw score (r=.60, p<.001). VIQ also showed a significant correlation with the number of correctly constructed designs (r=.20, p=.01) and the BD raw score (r=.18, p=.02).

The effect of age and IQ on BD task performance was further reported for each group (Table 7-11). No significant correlation was observed between the task measures and VIQ in each group (p>.05).

Table 7-11: Correlation between Block Design Task measures, age and VIQ for each Group

	Age*Num. Correct Design	VIQ* Num. Correct Design	Age* BD Raw Score	VIQ* BD Raw Score
ASD	.48*	.22	.58**	.21
ADHD	.61**	.10	.64**	.07
Comorbid	.57**	.04	.63**	.01
Control	.60**	.28	.66**	.24

** Correlation is significant at the 0.05 level, ** Correlation is significant at the 0.01 level.*

No difference in the magnitude of the correlation coefficients between groups was observed for the association between the task measures, age and VIQ (all p>.05).

7.5.2.4.3 Correlation of Task Measures with Clinical Measures

In order to see whether ASD/ADHD symptoms would affect the task performance, correlations between Block Design T-score (as a key index of BD performance) and clinical measures, including Conners score, SCQ and selective scores of SDQ (SDQ total score and SDQ hyperactivity) were explored.

Across all groups, Block Design T-score, showed only a significant correlation with Conners inattention (r_s=-.22, p=.01), suggesting poorer performance in those with higher symptoms of inattention.

The correlations were further explored in each group (see Table 7-12). In the control group, a significant correlation was observed for BD T-Score with SDQ total score (r=-.69, p=.002) and SDQ hyperactivity subscale (r=-.75, p<.001), suggesting the ones who had more hyperactivity traits as measured by SDQ performed worse in the Block Design task. The correlations

remained significant after covarying for age and VIQ. Moreover, Conners inattention was correlated with BD T-Score (r_s=-.35, p=.04).

No significant correlation was observed in the ASD group.

The ADHD group showed a moderate correlation between BD T-Score and SDQ total score (r=-.48, p=.004) and PACS hyperactivity (r=-.36, p=.02), indicating that those with higher hyperactivity and impulsivity symptoms had a poorer performance in Block Design task. The correlations remained significant after controlling for the effects of age and VIQ.

Finally, in the comorbid group the relationship between BD measures and autistic symptoms as well as ADHD symptoms was assessed. A significant correlation was observed between PACS inattention and BD T-Score (r=-.34, p=.01), suggesting that individuals who were more inattentive had a lower score on the BD task. The association remained significant after controlling for the effects of age and VIQ.

Table 7-12: Correlation between Block Design Task measures and clinical measures for each group (Unadjusted for age and VIQ)

	BD T-Score
Controls	
Conners Inattention	-.35*
Conners Hyperactivity/Impulsivity	-.30
SCQ	.05
SDQ Total	-.69**
SDQ Hyperactivity	-.75**
ASD	
Conners Inattention	-.13
Conners Hyperactivity/Impulsivity	.33
SCQ	-.08
SDQ Total	.13
SDQ Hyperactivity	-.09
ADHD	
Conners Inattention	-.06
Conners Hyperactivity/Impulsivity	-.06
SCQ	.11
SDQ Total	-.48*
SDQ Hyperactivity	.17
Comorbid	
Conners Inattention	-.01
Conners Hyperactivity/Impulsivity	.09
SCQ	.21
SDQ Total	.11
SDQ Hyperactivity	.28

**Correlation is significant at the 0.05 level,* ***Correlation is significant at the 0.01 level*

7.5.2.5 Discussion of the Block Design Task

Superior performance of individuals with ASD has been documented in the Block Design task (Happe, 1994b; Pellicano, et al., 2006; Ropar & Mitchell, 2001; Shah & Frith, 1993). Despite the high loading on nonverbal intelligence in the general population, performance on the BD subtest often has been reported to be inconsistent with general ability in individuals with ASD and peak performance in the Block Design, relative to other subtests has been frequently reported in the ASD literature (Happe, 1994b).

Contrary to expectations, the present sample did not find superior performance of high-functioning individuals with ASD in the BD task in terms of accuracy and score compared with controls. This finding is in line with some of the previous studies which failed to replicate the relatively good performance of individuals with Asperger's disorder or HFA in the BD task (Goldberg, et al., 2002; Kaland, et al., 2007; Ozonoff, Pennington, et al., 1991; Ozonoff, Rogers, & Pennington, 1991; Szatmari, et al., 1990). However, the current study design does not make it clear whether the ASD individuals had the same strategy to construct the blocks as control group or if they applied different techniques.

The inconsistent results of the BD Task across studies on ASD could be due to methodological issues such as different sample characteristics, for example, cognitive ability, age range, diagnosis and different versions of the BD task (Weschler versions vs. Shah and Frith's original Un/Segmented comparisons).

Although there are also studies that reported higher scores in the BD task in individuals with HFA compared to controls (Caron, et al., 2004; Mottron, 2004), most studies found superior performance in lower-functioning groups (Ropar & Mitchell, 2001; Shah & Frith, 1993). Moreover, the ones which used Shah and Frith's Un/Segmented design have found interesting results. For example, in a study by de Jonge et al. (2009) which used Un/Segmented version of the BD task, even though they did not find superior performance of individuals with ASD in terms of accuracy and RT, they found that they made significantly fewer errors during the reconstruction of the designs than control individuals. Their assumption was that individuals with superior mental segmentation abilities would place a block in the correct position within a design on the first placement; while in contrast, individuals with poorer mental segmentation skills would more frequently place a block in an incorrect position initially and adjust it subsequently during the process of reconstruction. The authors concluded that the superiority of ASD individuals was reflected in the condition that relies most on mental segmentation ability: the ability to decide exactly how and in which direction a double-coloured block must be positioned within a design (de Jonge, et al., 2009).

Therefore, it seems that if the current study had administered the Un/Segmented design as in de Jonge's study, it would likely to find the differences in the strategy that individuals with ASD were applying to construct the blocks.

This superior performance has been explained by a specific asset in mentally segmenting the designs. This was shown in an experiment by Shah and Frith using Un/Segmented Block Design. They found that presegmenting the design to be copied helped control groups significantly more than it helped participants with ASD (Shah & Frith, 1993). This suggested that the individuals with ASD readily perceived the designs in terms of their constituent parts and were not locked into the strong 'gestalt' of the design.

The only difference that was found in the current sample was the poorer performance of the ADHD group compared with the other three groups. However, it seems that their lower score and poorer performance could be explained mainly by their lower cognitive ability as when the IQ was controlled for, the group differences disappeared. Moreover, it was shown that the higher hyperactivity and impulsivity symptoms were associated with poorer performance in the BD task in the ADHD group.

Interestingly, the comorbid group performed relatively similarly to the ASD group in the BD task and they exhibited better performance than the ADHD group. However, it is not clear whether this superior performance was due to their autistic symptoms and therefore was rooted in a WCC style.

7.5.2.6 Conclusion

In summary, a weak drive for central coherence in individuals with ASD has not been confirmed in the present sample of individuals with HFA/Asperger's using the BD task which could be due to different sample characteristics and methodological issues.

The only difference that was found in the current sample was the poorer performance of the ADHD group compared with the other three groups which appeared to be mediated by their lower cognitive ability.

7.5.2.7 Limitations and Suggestions for Future Research

The present study has a number of limitations. First, the sample size, although comparable to previous studies, was relatively small and unequal, and the participants' age range was quite wide. However, compared to studies that found superior BD performance in their ASD group, the size of the present sample was not smaller.

It is suggested that future research apply the Un/Segmented design originally suggested by Shah and Frith (Shah & Frith, 1983), as this would give them the potential to explore the strategy that different individuals apply to construct the blocks.

Moreover, in the current study the reconstruction time was not reported directly; instead, the BD raw score was reported which is a reflection of both accuracy and the time taken to reconstruct each design. However, the reconstruction time might uncover the subtle differences between ASD and other groups.

7.5.3 Experiment 3: Sentence Completion Task

This task was taken from Happé and employed the same design she used in her study in 2001 (Happe, Briskman, & Frith, 2001). It is a simple and easy-to-administer verbal task that assesses whether individuals use the preceding sentence context in order to complete the sentence in a meaningful way or if they have a tendency to process the sentence locally and provide a response which is only coherent in a fragment of the sentence rather than the sentence as a whole.

This task has been shown to be sensitive to individual differences among children with ASD (Booth & Happe, 2010), young adults with ASD (Losh et al., 2009), and parents of boys with ASD (Happe, et al., 2001).

7.5.3.1 Method

The Sentence Completion task consists of 14 sentences (see Appendix F), of which 10 are designed to invite a local completion, at odds with the global coherence of the sentence in individuals with WCC (Booth & Happe, 2010). For example, *'You can go hunting with a knife and …'* can attract *'fork'* as a local response to the sentence. This response is locally coherent with the final two words in isolation but is incongruent in the context of the whole sentence, whereas globally meaningful completions such as *'gun'* show intact or strong coherence.

The other 4 sentences were used as filler items without bringing up this aspect of local–global conflict (e.g., *'I was given a pen and . . .'*).

7.5.3.2 Procedure

The sentences were read aloud to the participants by the experimenter and they were instructed to say something to finish each sentence. Completions produced by participants could be single words or phrases. A practice filler sentence was administered first: *'He cleaned up the mess with a brush and …'* to make them familiar with the task. Responses were written down by the experimenter and audiotaped for later scoring.

7.5.3.3 Scoring

All scoring was based on participants' first complete response and was calculated according to the guidelines provided by Booth and Happé (Booth & Happe, 2010). Two performance variables were scored for each participant: a completion score and the number of local responses.

Completion score: A 3-point scoring system was used to capture the range of responses that were produced for the 10 test sentence stems: 2 points assigned for a globally meaningful completion; 1 point assigned when the response was an 'odd' completion to the sentence but not an obviously local completion (e.g., a repetition or local association to another word in the sentence), or when no response was provided (e.g., 'don't know'); and 0 points assigned for local responses.

A local response was defined as a completion that could be expected as a response to the final two words in isolation and did not make sense in the context of the whole sentence. An example of a local response to the stem *'The sea tastes of salt and . . .'* would be *'pepper'* whereas *'water'* would not be scored as a local error (even though '*salt and water*' might be considered as associates) because this response is appropriate to the meaning of the whole sentence. See Appendix F for scoring examples. The completion score ranged from 0 to 20. The scoring system was quite conservative as responses were not scored as a local completion if they could make sense in the whole sentence context. Thus, a completion such as *'The shoemaker mended the shoes and . . . laces'* was not scored as local because it makes sense in the context of the whole sentence even though it likely reflects attention to the final words of the stem and a relatively local processing style.

Two raters scored all the sentences. Overall agreement was high (95%, kappa=.83), and disagreements were resolved between the two raters during a consensus meeting.

7.5.3.4 Hypotheses

Given the weak central coherence drive in ASD, higher local completion score was expected in the ASD group compared to the control group. It was also predicted that a strong association would be present between the number of local completions and clinical measures of autistic behaviour.

There is one study that has compared ASD and ADHD groups on Sentence Completion. It reported that the ASD group produced significantly more local completions than the ADHD group (Booth & Happe, 2010). Based on this study, a greater tendency for local completion was expected in the ASD group compared with the ADHD group. Moreover, it was predicted that individuals with ADHD would perform poorer than controls due to inattention and impulsivity.

No prediction was made regarding the comorbid group's performance and exploratory analyses were conducted to assess whether individuals with comorbid ASD-ADHD showed a tendency for local completions.

7.5.3.5 Results from the Sentence Completion Task

Data were available from 115 individuals including 19 ASD, 34 ADHD, 42 comorbid, and 20 controls. Group descriptive for these individuals are presented in Table 7-13.

No significant differences in age among the groups (p>.05) were observed. However, significant differences were found for FSIQ, PIQ, and VIQ (all p<.05). Further analysis showed that the two groups of children with ADHD symptomatology (pure ADHD and comorbid groups) had significantly lower FSIQ, PIQ, and VIQ compared to controls (LSD post-hoc tests, p<.05), whereas the ASD group did not differ from controls (all p>.05). In addition, the ASD group had a significantly higher FSIQ relative to the ADHD group (p<.05). However, no differences amongst the clinical groups were observed for PIQ and VIQ (all p>.05).

Table 7-13: Group descriptive for participants who completed the Sentence Completion Task: Means (SD), [Range]

	ASD (N=19)	ADHD (N=34)	Comorbid (N=42)	Controls (N=20)	$F_{(3,111)}$	P	Post-hoc LSD
Age in month	133.42(19.70)	132.97(32.08)	127.58 (25.51)	125.10(29.59)	.54	.61	
[Range]	[96-168]	[84-191]	[87-200]	[91-180]			
FSIQ	111.47(15.98)	100.88(14.32)	105.64 (13.14)	121.60(13.65)	9.90	<.001	Controls> ADHD, Comorbid*
[Range]	[77-139]	[70-135]	[79-142]	[102-149]			ASD>ADHD*
PIQ	108.05(14.54)	99.18(14.01)	104.19 (13.22)	115.25(12.77)	6.21	.001	Controls> ADHD, Comorbid*
[Range]	[80-136]	[64-131]	[75-141]	[100-141]			
VIQ	112.47(18.47)	102.53(16.09)	105.79 (14.57)	123.00(14.67)	8.09	<.001	Controls> ADHD, Comorbid*
[Range]	[78-145]	[75-133]	[77-146]	[99-151]			

** Post-hoc test, p<.05*

7.5.3.5.1 Group Comparisons in the Sentence Completion Task

Initially, analyses were conducted without adjusting for age and IQ. Group differences were explored using ANOVA with group as the between-subjects factor (see Table 7-14).

Individuals in the control group had a significantly higher completion score than the three clinical groups ($F_{(3,111)}$=3.03, p=.03, η^2=0.076 with the post-hoc LSD p=.007 for control-ASD, p=.02 for control-ADHD, and p=.01 for control-comorbid comparisons). No significant differences were observed for the completion score between clinical groups (p>.05). Moreover, the control group produced significantly fewer local completions than the three clinical groups ($F_{(3,111)}$=3.09, p=.03, η^2=0.077 with the post-hoc LSD p=.008 for control-ASD, p=.02 for control-ADHD, and p=.01 for control-comorbid comparisons). Again, no significant differences were observed for the completion scores between the clinical groups (p>.05).

The effect sizes were calculated for pairwise comparisons (Table 7-15). As is shown, the effect sizes for the comparisons between each of the clinical groups and controls were quite high for both completion scores and the number of local responses.

Figure 7-3 shows the percentage of participants in each group who produced local responses divided into three categories: two or more, one, or no local responses. It is clear that the three clinical groups performed at the same level in the Sentence Completion Task in terms of completion score and number of local responses, whereas the control group showed a completely different pattern of performance.

Table 7-14: Group comparisons on Sentence Completion Task: Means (SD)

	ASD (N=19)	ADHD (N=34)	Comorbid (N=42)	Control (N=20)	Group effect		Post-hoc LSD
					$F_{(3,111)}$	P	
Number of Local Completions	1.74(1.85)	1.47(1.35)	1.48(1.64)	0.45(0.69)	3.09	.03	Controls< ASD, ADHD, Comorbid*
Completion Score	16.00(3.64)	16.62(2.77)	16.55(3.41)	18.65(1.75)	3.03	.03	Controls> ASD, ADHD, Comorbid*

** Post-hoc test, p<.05*

Table 7-15: Effect sizes (d) of the Sentence Completion Task

	Control-ASD	Control-ADHD	Control-Comorbid	ASD-ADHD	ASD-Comorbid	Comorbid-ADHD
Number of Local Completions	-.93	-.96	-.82	.17	.15	.007
Completion Score	.93	.88	.77	-.19	-.15	-.02

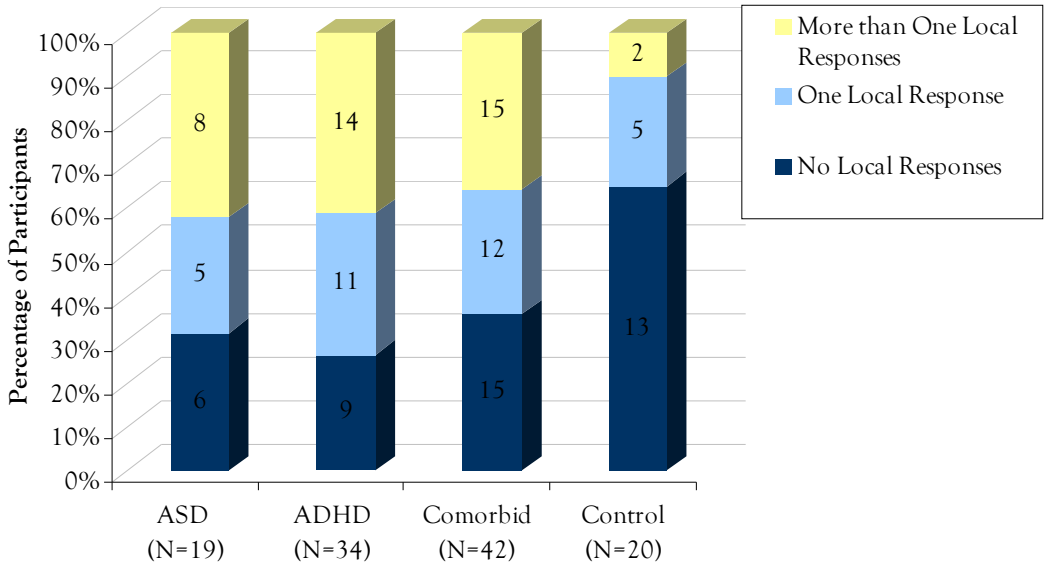


Figure 7-3: Percentage (and n) of participants producing Local Completions in the Sentence Completion Task

All the above analyses were repeated adjusting for age and IQ. As the Sentence Completion task was verbally demanding, the effect of VIQ was evaluated instead of FSIQ. ANCOVA was run on the task variables with group as the between-subjects variable and age and VIQ as covariates. When adjusted for age, the findings did not differ. When adjusted for VIQ, the findings differed from the unadjusted analysis. This time, the significant group effect for the total number of local completions ($F_{(3,110)}$=2.01, p=.12, η^2=0.052) and completion score ($F_{(3,110)}$=1.95, p=.13, η^2=0.051) disappeared. In addition, both age and VIQ were entered as covariates. The findings were similar to when only VIQ was a covariate; therefore, in order to prevent repetition, the result was not reported.

ANOVA is quite a robust test which reduces the risk of Type I error in multiple comparisons. However, reducing the risk of making a Type I error increases the chance of making a Type II error (i.e., incorrectly deducing no difference, when in fact there is a significant difference). Based on this and also based on the hypothesis that individuals with ASD have a tendency for local completions compared to controls, it was decided to look at the two groups comparisons as well.

Significant group differences were observed between ASD and control groups for total number of local completions ($F_{(1,36)}$=5.11, p=.03) and for completion score ($F_{(1,36)}$=4.84, p=.03) even after covarying for VIQ; the ASD group also showed a higher number of local completions and a lower completion score. Comparison between comorbid and control groups also revealed that the comorbid group had a significantly higher number of local completions ($F_{(1,59)}$=4.77, p=.03) and a lower completion score ($F_{(1,59)}$=3.83, p=.05) than controls even after controlling for VIQ.

Moreover, individuals with ADHD showed a higher number of local completions ($F_{(1,51)}$=4.77, p=.03) and a trend for lower completion score ($F_{(1,51)}$=3.67, p=.06) than controls even after controlling for VIQ.

7.5.3.5.2 Effects of Age and IQ

Overall, across the groups, there was a mild correlation between age and VIQ with the Sentence Completion Task measures (see Table 7-16). The effect of age and VIQ on the Sentence Completion Task was further explored for each group. No significant correlation was observed in the control and ADHD groups. In the ASD group, there was only a significant effect of VIQ on the number of local completions (r=-.39, p=.04) and completion score (r=.42, p=.04). Finally, in the comorbid group, only a significant effect of age on the number of local completions (r=-.28, p=.03) and completion score (r=.31, p=.02) was observed.

However, when the magnitude of correlations between task measures, age and VIQ were explored by Fisher's r-to-z transformation, no differences between the groups were observed (all p>.05).

Table 7-16: Correlation between Sentence Completion Task measures, age and VIQ

	Number of Local Completions	**Completion Score**
Age	-.19*	.22**
VIQ	-.21*	.22**

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level.*

7.5.3.5.3 Correlations between Task Measures and Clinical Measures

In order to see whether ASD/ADHD symptoms would affect the task performance, correlations between Sentence Completion task measures and clinical measures including Conners score, SCQ and selective scores of SDQ (SDQ total score and SDQ hyperactivity) were conducted across all groups (see Table 7-17) and within each group (see Table 7-18).

Table 7-17: Correlation between Sentence Completion Task measures and clinical measures across all groups

	Conners Inattention	**Conners Hyperactivity /Impulsivity**	**SCQ**	**SDQ Total**	**SDQ Hyperactivity**
Number of Local Completions	.34**	.10	.22*	.11	.07
Completion Score	-.31**	-.09	.23*	-.09	-.08

**Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level*

In the control group, no significant correlation was observed between the Sentence Completion Task variables and clinical measures (all $p>.05$).

In the ASD group, there was a moderate correlation between Conners inattention and the number of local completions ($r_s=.45$, $p=.03$) and the completion score ($r_s=-.49$, $p=.02$), suggesting a tendency for local completions in those who were more inattentive. Moreover, a moderate correlation was observed between RRIB as measured by the ADOS and the number of local completions ($r=.48$, $p=.02$) and the completion score ($r=-.51$, $p=.02$), indicating a tendency for local completion in those with higher restricted/repetitive behaviours. The correlation remained significant after covarying for age and VIQ.

The ADHD group showed a moderate correlation for Conners inattention and the number of local completions ($r_s=.33$, $p=.03$) and the completion score ($r_s=-.30$, $p=.04$). In addition, there was a moderate correlation between Conners hyperactivity/impulsivity and the number of local completions ($r_s=.29$, $p=.04$), suggesting a tendency for local completion in those who were more inattentive and impulsive.

Finally, in the comorbid group, the relationship between the Sentence Completion Task measures and autistic symptoms as well as ADHD symptoms was assessed. A significant correlation was observed for Conners hyperactivity/impulsivity and the number of local completions ($r_s=.30$, $p=.03$) and the completion score ($r_s=-.29$, $p=.03$). Moreover, a moderate correlation was observed between RRIB as measured by ADOS and the number of local completions ($r=.32$, $p=.02$) and the completion score ($r=-.31$, $p=.03$). The correlations remained significant after covarying for age and VIQ.

Table 7-18: Correlation between Sentence Completion Task measures and clinical measures for each group (Unadjusted for age and VIQ)

	Number of Local Completions	Completion Score
Controls		
Conners Inattention	.14	-.28
Conners Hyperactivity /Impulsivity	-.14	.23
SCQ	.07	.007
SDQ Total	.10	-.12
SDQ Hyperactivity	.09	-.16
ASD		
Conners Inattention	.45*	-.47*
Conners Hyperactivity /Impulsivity	.27	-.28
SCQ	.14	-.21
SDQ Total	-.03	-.02
SDQ Hyperactivity	.03	-.08
ADHD		
Conners Inattention	.33*	-.30*
Conners Hyperactivity /Impulsivity	.29*	-.26
SCQ	.17	-.11
SDQ Total	.18	-.008
SDQ Hyperactivity	-.06	.08
Comorbid		
Conners Inattention	.04	.02
Conners Hyperactivity /Impulsivity	.30*	-.29*
SCQ	.06	-.11
SDQ Total	-.17	.20
SDQ Hyperactivity	-.02	.11

**Correlation is significant at the 0.05 level,* ***Correlation is significant at the 0.01 level*

7.5.3.6 Discussion of the Sentence Completion

A disregard for sentence context and a weak central coherence style in individuals with ASD has been previously demonstrated in the Sentence Completion Task (Booth & Happe, 2010). Furthermore, this study compared individuals with ADHD to those with ASD on this measure and found local errors were specific to those with ASD (Booth & Happe, 2010). However, no study has directly compared the performance of ASD individuals with a group of comorbid ASD and ADHD individuals.

The weak coherence style in ASD has been confirmed in the current sample as the ASD group made significantly more local completions to the test stems and had a lower completion score than the age- and IQ-matched controls. This was the case even though the absolute number of local completions was low (due in part, perhaps, to conservative scoring).

However, in the present sample the clinical groups all performed at the same level and no differences were found between the two groups with ADHD (i.e. the pure and comorbid group) and the ASD group. Individuals with ADHD also showed a WCC style on the Sentence Completion Task. This is in contrast to the findings of the Booth and Happé study (Booth & Happe, 2010) and thus raises doubt as to the specificity of WCC style to the ASD group.

The significant correlation between VIQ and Sentence Completion Task performance was observed across all groups. However, it appeared that the tendency of the clinical groups to provide local completions was not purely influenced by cognitive and verbal ability as a difference between clinical groups and controls was evident, though attenuated, even after controlling for VIQ. This therefore suggests that the Sentence Completion Task taps individual differences in cognitive style rather than merely ability.

Further exploration of the data suggests that approximately a third of the ASD group did not make any local completions. This may reflect the heterogeneity within the ASD sample. Moreover, it is accepted that weak coherence may only be present in a proportion of those with the disorder and does not characterise all individuals with ASD.

Local completions in the Sentence Completion Task may reflect either enhanced attention to local features or a reduced tendency to integrate all elements of the sentence. In the present sample, it was revealed that both symptoms of inattention and social impairments were associated with a higher tendency for local completions, regardless of diagnostic groups.

In the ADHD group, inattention and hyperactivity/impulsivity symptoms were associated with a more detail-orientated performance. In the ASD group, inattention and restricted, repetitive interests and behaviours, and in the comorbid group, hyperactivity/impulsivity symptoms and restricted, repetitive interests and behaviours, were related to a WCC style.

7.5.3.7 Conclusion

The Sentence Completion Task is a simple and easy to administer test which appears to be a useful measure of CC capable of assessing local processing bias. It proved to be sensitive to individual differences between the ASD and control groups. However, it failed to show the specificity of WCC in ASD in the present sample as both the ADHD and comorbid groups showed the same style as the ASD group.

Even though, the three clinical groups exhibited the same style in their performance, it seems as if a weak drive for CC in each group had different underlying reasons.

7.5.3.8 Limitations and Suggestions for Future Research

The current study presented novel data considering the co-occurrence of ADHD and ASD. However, it had a number of limitations. First, the subgroup sample sizes were relatively small and unequal, and the participants' age range was quite wide.

It is suggested that future research reassess the WCC style and its specificity to ASD by comparing the performance of individuals with ASD to alternative control groups such as individuals with ADHD using a larger sample. In addition, in the current design, the stems were presented in a fixed order; however, as Booth et al. recommended in their study (Booth & Happe, 2010), future research should administer a counterbalanced order of stems to assess item effects and to establish whether filler stems (for which local completions were also globally congruent) encouraged local completions on proceeding test stems.

7.6 Chapter Summary

The current chapter explored the WCC account using the EFT and the BD task in the visuo-spatial domain, and the Sentence Completion task in the verbal-semantic domain.

In the EFT, the weaker drive for central coherence in individuals with ASD was not confirmed, which could have been due to the different sample characteristics and methodological issues. It was revealed that the pattern of performance in the comorbid group was to a large extent similar to the ADHD group (i.e. faster responses and higher rate of false claims) which in turn would suggest that quicker RT in EFT in ASD, reported in previous studies, could be to some extent due to the unmeasured comorbid ADHD symptoms.

The BD task could not reveal a weak drive for CC in individuals with ASD. The only difference that was found in the current sample was the poorer performance of the ADHD group compared with the other three groups, which appeared to be mediated by their lower cognitive ability. The comorbid group performed relatively similarly to the ASD group in the BD task and they exhibited better performance than the ADHD group.

In the verbal-semantic domain, the Sentence Completion task proved to be sensitive to individual differences between the ASD and control groups. However, it failed to show a specificity of WCC to ASD as both ADHD and comorbid groups showed the same local completion style similar to the ASD group. Even though, the three clinical groups exhibited the same style in their performance, it seems as if there were different underlying reasons behind a weak drive for CC in each group.

Chapter 8

Quantitative Approach

8.1 Chapter Overview

As discussed in Chapter 1, there is evidence that both autistic and ADHD traits are continuously distributed in the general population and ASD and ADHD as disorder, represents the extreme of a normally distributed continuum.

It is increasingly recognised, therefore, that there is a need to study dimensional as well as categorical constructs of the phenotype. Thus, based on this view, the current chapter adopts a quantitative approach.

8.1.1 Broader Autism Phenotype

Autism has traditionally been considered as a qualitatively distinct behavioural syndrome characterised by triad of impairments. There is, however, consistent evidence that autistic traits are continuously distributed in the general population and ASD represents the extreme of a normally distributed continuum (Hoekstra, et al., 2007; Steer, et al., 2010; Wheelwright, et al., 2010).

Relatives of individuals with ASD show elevated levels of autistic traits (Bishop, Maybery, Wong, Maley, & Hallmayer, 2006) suggesting that subclinical autistic traits share familial influences with diagnosed ASD. Furthermore, common genetic variants that are present in a significant proportion of the general population are thought to play a role in the aetiology of autism (Campbell et al., 2006; Chakrabarti & Fombonne, 2005; Ronald et al., 2010).

The genetic theory of autism proposes that autism is strongly heritable and that first-degree relatives of children with autism possess the BAP (Bailey, et al., 1995). The BAP is generally considered to be a subclinical set of characteristics or traits that index familiality and/or genetic liability to autism. It is regarded to be milder but qualitatively similar to the diagnosed autism phenotype (Wheelwright, et al., 2010).

BAP was first noted by Kanner (Kanner & Eisenberg, 1957), and were also mentioned in Folstein and Rutter's early twin study which found a higher concordance rate for a more broadly defined cognitive impairment (Folstein & Rutter, 1977b). Bolton et al. explored family history data and reported that autism phenotype extends beyond autism as traditionally diagnosed (Bolton et al., 1994).

8.1.2 ADHD: Quantitative Traits

ADHD, as defined by DSM-IV, is a dichotomous trait making up a distinct diagnostic category. There is, however, consistent evidence that measures of activity, impulsivity, and inattention, are continuously distributed in the general population and there are suggestions that ADHD represents the extreme of normally distributed traits rather than categorically distinct conditions.

For example, population twin studies have found similar estimates of heritability using categorical diagnoses (Goodman & Stevenson, 1989; Thapar, et al., 2000) as quantitative rating-scale measures of ADHD (Biederman, et al., 1993; Boyle, et al., 1997). Moreover, it has been shown in both twin and sibling studies that the genetic contribution to ADHD is the same across the continuum and in the extreme ADHD scores (Chen, et al., 2008; Levy, et al., 1997).

Community cohorts and twin samples have measured ADHD symptoms using dimensional symptom scales and found individual differences as continuously distributed quantitative traits. These studies suggest that genetic risk factors for ADHD also influence levels of ADHD symptoms throughout the population (Stevenson et al., 2005).

Furthermore, in longitudinal follow-up studies, the adverse outcomes predicted by dimensionally defined 'severity' were similar to those predicted by clinically defined 'ADHD cases' (Chen & Taylor, 2005).

Taken all together, these studies suggest that clinical ADHD should be regarded as the extreme end of these quantitative traits rather than as a discrete category (Levy, et al., 1997).

8.1.3 Summary

In previous chapters, the relationship between clinical measures and cognitive task measures were assessed and a number of significant associations were identified. In this chapter, the focus is to consider these associations in more depth applying multivariate analysis in order to find out the extent to which the cognitive measures are associated with behavioural manifestations.

The current chapter adopts a quantitative approach, which assumes that ADHD and ASD are at the extreme end of continuously distributed traits as are the underlying cognitive processes, so that findings from all investigations apply equally to the clinical diagnosis and the extreme end of the ASD-like and ADHD-like traits in the general population (i.e. the control group).

8.1.4 Methods

In order to further investigate the predictive accuracy of ASD and ADHD traits for different tasks were administered in this study, separate backward multiple regressions were conducted. Autistic symptoms (SCQ scores) and ADHD symptoms (Conners scores) were included in the analyses with age.

The analysis began with a full model and variables were eliminated in an iterative process. After the elimination of each variable the fit of the model was tested, this enabled separate regression analyses to identify the variables that significantly contributed to the tasks' variables. For all the regression analysis, standardized beta is reported. Also regression was run with and without FSIQ entering in the model.

8.1.5 Results

The full regression model is presented for each task separately in the table format. In order not to be repetitive, the Beta coefficients in the text are reported where ASD and ADHD symptoms and age were entered as predictors; while the tables demonstrate the Beta coefficients where FSIQ were also entered in the model.

8.1.5.1 GO/No-Go Task

Table 8-1 shows Beta coefficients from a stepwise linear regression with backward removal predicting Go/No-Go task outcome from ASD and ADHD symptoms. The analysis showed that age was the only significant predictor of reaction time (β=-.49, t=-5.88, p<.001) explaining 24.1% of the variance. Age (β=-.40, t=-4.72, p<.001) and Conners inattention (β=.21, t=2.51, p=.01) were significant predictors of RT variability ($F_{(2,108)}$=15.48, p<.001), accounting for 22.3% of the variance.

Age (β=-.26, t=-3.03, p=.003) and Conners hyperactivity/impulsivity (β=.33, t=3.75, p<.001) were significant predictors of premature responses ($F_{(2,108)}$=12.76, p<.001), accounting for 19.1% of the variance. Conners inattention (β=.24, t=2.58, p=.01) was revealed to be the only significant predictor of commission errors, accounting for 5.8% of the variance.

For omission errors, age (β=-.20, t=-2.20, p=.03) and Conners inattention (β=.20, t=2.21, p=.03) were accounted for 9% of the variance ($F_{(2,108)}$=5.34, p=.006).

The results did not change when FSIQ entered in the above regression models.

8.1.5.2 Antisaccade Task

Table 8-2 shows Beta coefficients from a stepwise linear regression with backward removal predicting antisaccade task outcome from ASD and ADHD symptoms. Age (β=-.43, t=-4.48, p<.001) was found to be the only significant predictor of antisaccade latency, accounting for 18.2% of the variance. Conners inattention (β=.34, t=3.67, p=.001) was the significant predictor of antisaccade RT variability, explaining 11.8% of the variance of RT variability.

Age was the only significant predictor for antisaccade velocity (β=-.33, t=-3.75, p=.001) and for error rate (β=-.52, t=-6.30, p=.001); accounting for 11.2% and 26.9% of the variance; respectively.

Finally, age (β=.33, t=3.74, p<.001) and Conners inattention (β=-.26, t=-2.86, p=.005) were the significant predictors for antisaccade correction rate ($F_{(2, 102)}$=11.13, p<.001), accounting for 17.9% of the variance.

None of the clinical measures, age or FSIQ could predict saccade amplitude in antisaccade task. The results did not change when FSIQ entered in the above regression models except for the error rate which this time, the effect of age (β=-.57, t=-6.91, p<.001) and FSIQ (β=-.21, t=-2.59, p=.01) was shown to be significant ($F_{(2,107)}$=24.22, p<.001), explaining 31.2% of the variance.

8.1.5.3 Prosaccade Task

Table 8-3 shows Beta coefficients from a stepwise linear regression with backward removal predicting prosaccade task outcome from ASD and ADHD symptoms. None of the clinical measures showed significant results when entered in the regression model for prosaccade latency, RT variability, amplitude, or velocity. However, when FSIQ added to the model, it turned out that FSIQ was the significant predictor of latency (β=.23, t=2.32, p=.02) and velocity (β=.22, t=2.44, p=.02); explaining 23.2% and 5.2% of the variance; respectively.

8.1.5.4 Triangle Task

Table 8-4 shows Beta coefficients from a stepwise linear regression with backward removal predicting Triangle task outcome from ASD and ADHD symptoms. For G-D appropriateness score, age (β=.23, t=2.44, p=.02) was the only significant predictor explaining 5.3% of the variance. No differences were observed when the FSIQ entered in the regression model.

None of the clinical measures, age or FSIQ could predict G-D intentionality score.

Age (β=.39, t=4.44, p<.001) was found to be significant predictor of ToM intentionality score accounting for 15.5% of the variance. Entering FSIQ in the regression model did not change the findings.

Also, age (β=.42, t=4.58, p<.001) and FSIQ (β=.26, t=2.88 p=.005) were the significant predictors of ToM appropriateness score ($F_{(2,106)}$=11.84, p<.001), explaining 18.3% of the variance.

8.1.5.5 Strange Stories Task

Table 8-5 shows Beta coefficients from a stepwise linear regression with backward removal predicting Strange Stories task outcome from ASD and ADHD symptoms. Regression analysis in Strange Stories task revealed that age (β=.24, t=2.33, p=.02) and Conners inattention (β=-.32, t=-3.05, p=.001) were found to be significant predictors of mental state stories ($F_{(2,78)}$=7.87, p=.001), accounting for 16.8% of its variance. However, when FSIQ entered in the model, the result changed and Conners inattention was no longer a significant predictor. This time only the

effect of age (β=.44, t=4.94, p<.001) and FSIQ (β=.62, t=6.91, p<.001) was significant ($F_{(2,78)}$=28.47, p<.001), explaining 42.2% of the variance.

Age (β=.56, t=6.34, p<.001) and Conners inattention (β=-.22, t=-2.47, p=.02) were found to be significant predictors of physical state stories ($F_{(2,78)}$=24.28, p<.001), accounting for 38.4% of its variance. However, when FSIQ entered in the model, the result changed and Conners inattention was no longer a significant predictor. This time only the effect of age (β=.67, t=7.44, p<.001) and FSIQ (β=.31, t=3.44, p=.001) was significant ($F_{(2,78)}$=28.56, p<.001), explaining 42.3% of the variance.

8.1.5.6 Cueing Task

Table 8-6 shows Beta coefficients from a stepwise linear regression with backward removal predicting cueing task outcome from ASD and ADHD symptoms. Regression analysis was carried out for Cueing task and revealed that age was the only significant predictor of saccade latency (β=-.19, t=-2.02, p=.04) and SRT variability (β=-.35, t=-3.90, p<.001). However, it could only explain 3.7% of the variance in latency and 12.6% of the variance in SRT variability.

Conners hyperactivity was the only significant predictor of percentage of anticipatory saccade (β=.27, t=2.88, p=.005), accounting for 7.2% of its variance.

None of the clinical measures, age or FSIQ could predict saccade amplitude or correction during the cue period, in Cueing task.

The results did not change when FSIQ entered in the above regression models.

8.1.5.7 Embedded Figures Task

Table 8-7 shows Beta coefficients from a stepwise linear regression with backward removal predicting EFT outcome from ASD and ADHD symptoms. Age (β=.31, t=3.40, p=.001) was found to be significant predictor of accuracy in EFT accounting for 9.4% of the variance. Entering FSIQ in the regression model did not change the findings.

For false claim, age (β=-.32, t=-3.83, p<.001) and Conners inattention (β=.33, t=3.93, p<.001) were found to be significant predictors ($F_{(2,110)}$=16.17, p<.001), accounting for 22.7% of its variance. However, when FSIQ entered in the model, the result changed and Conners inattention was no longer a significant predictor. This time only the effect of age (β=-.47, t=-5.80, p<.001) and FSIQ (β=-.47, t=-5.72, p<.001) was significant ($F_{(2,110)}$=25.99, p<.001), explaining 32.1% of the variance.

Finally, age (β=-.27, t=-3.07, p=.003) and Conners hyperactivity/impulsivity (β=-.28, t=-3.25, p=.002) were found to be significant predictors of reaction time as measured in response to correct responses ($F_{(2,78)}$=10.63, p<.001), accounting for 16.2% of the variance. Entering FSIQ in the regression model did not change the findings.

8.1.5.8 Block Design

Table 8-8 shows Beta coefficients from a stepwise linear regression with backward removal predicting BD task outcome from ASD and ADHD symptoms. Regression analysis revealed that Conners inattention was the only predictor of Block design T-score (β=-.52, t=-3.91, p<.001). However when FSIQ entered in the model, the result changed and Conners inattention was no longer a significant predictor. This time only the effect of FSIQ (β=.72, t=8.73, p<.001) was significant, accounting for 48.2% of its variance.

8.1.5.9 Sentence Completion Task

Table 8-9 shows Beta coefficients from a stepwise linear regression with backward removal predicting Sentence Completion task outcome from ASD and ADHD symptoms. The number of local completions in the Sentence completion task was only predicted by Conners inattention (β=.30, t=3.32, p=.001), reflecting the higher inattention score, the higher the local completion. It was accounting for 9% of the local completion variance. The result did not change when FSIQ entered in the above regression models.

Table 8-1: Beta coefficients from a stepwise linear regression with backward removal predicting Go/No-Go task outcome from ASD and ADHD symptoms, and age for the whole sample

Mean RT(msec)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.13	-.13	-.13	-.10	Removed
Conner Inattention	-.01	-.009	Removed	-	-
Conner Hyper/Impulsivity	.004	Removed	-	-	-
Age	-.52**	-.52**	-.52**	-.49**	-.49**
FSIQ	-.13	-.13	-.13	Removed	-
RT Variability	**Model 1**	**Model 2**	**Model 3**	**Model 4**	
SCQ	-.19*	-.17*	-.18	Removed	
Conner Inattention	.18	.24*	.29*	.21*	
Conner Hyper/Impulsivity	.09	Removed	-	-	
Age	-.43**	-.42**	-.39**	-.40**	
FSIQ	-.11	-.11	Removed	-	
Premature Responses	**Model 1**	**Model 2**	**Model 3**	**Model 4**	
SCQ	.10	.10	.105	Removed	
Conner Inattention	.10	.11	Removed	-	
Conner Hyper/Impulsivity	.18	.21	.28**	.33**	
Age	-.30**	-.28**	-.27**	-.27**	
FSIQ	-.06	Removed	-	-	
Commission Errors (%)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	.008	Removed	-	-	-
Conner Inattention	.16	.17	.16	.22*	.24*
Conner Hyper/Impulsivity	-.01	-.01	Removed	-	-
Age	-.22*	-.22*	-.22*	-.17*	Removed
FSIQ	-.15	-.15	-.15	Removed	-
Omission Errors (%)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.13	-.13	Removed	-	
Conner Inattention	-.22*	-.22*	-.24*	-.23**	
Conner Hyper/Impulsivity	.01	Removed	-	-	
Age	-.27**	-.27**	-.28**	-.30**	
FSIQ	.14	.15	.10	Removed	

Note: β coefficients are standardised, *$p<0.05$, ** $p\leq0.01$

Table 8-2: Beta coefficients from a stepwise linear regression with backward removal predicting Antisaccade task outcome from ASD and ADHD symptoms, FSIQ and age for the whole sample

AS Latency (msec)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	.04	.04	.03	Removed	-
Conner Inattention	-.05	-.05	Removed	-	-
Conner Hyper/Impulsivity	.20	.20	.17	.18	Removed
Age	-.44**	-.43**	-.42**	-.42**	-.42**
FSIQ	-.02	Removed	-	-	-
AS RT Variability	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	.06	.05	.05	Removed	-
Conner Inattention	.39*	.40*	.40*	.40**	.34**
Conner Hyper/Impulsivity	-.12	-.11	-.10	-.08	Removed
Age	-.05	-.04	Removed	-	-
FSIQ	-.05	Removed	-	-	-
AS Velocity (º/s)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	
SCQ	-.10	-.11	-.09	-.10	Removed
Conner Inattention	-.05	Removed	-	-	-
Conner Hyper/Impulsivity	.09	.06	Removed	-	-
Age	-.32**	-.32**	-.32**	-.33**	-.33**
FSIQ	.05	.06	.04	Removed	-
AS Amplitude (º)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	.009	Removed	-	-	-
Conner Inattention	-.03	-.03	Removed	-	-
Conner Hyper/Impulsivity	-.08	-.08	-.10	-.08	Removed
Age	-.17	-.16	-.16	-.14	-.14
FSIQ	-.06	-.06	-.06	Removed	-
AS Error Rate (%)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.008	-.008	-.009	Removed	
Conner Inattention	-.001	Removed	-	-	
Conner Hyper/Impulsivity	-.002	-.002	Removed	-	
Age	-.57**	-.57**	-.57**	-.57**	
FSIQ	-.22*	-.22*	-.22*	-.21*	
AS Correction Rate (%)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	.06	.05	.06	Removed	
Conner Inattention	-.23	-.26*	-.28*	-.26*	
Conner Hyper/Impulsivity	-.04	Removed	-	-	
Age	.34**	.34**	.33**	.33**	
FSIQ	.04	.04	Removed	-	-

Table 8-3: Beta coefficients from a stepwise linear regression with backward removal predicting Prosaccade task outcome from ASD and ADHD symptoms, and age for the whole sample

PS Latency (msec)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	.04	.04	.04	Removed	-
Conner Inattention	.03	.03	Removed	-	-
Conner Hyper/Impulsivity	.14	.14	.16	.17	Removed
Age	-.02	Removed	-	-	-
FSIQ	.24*	.25*	.24*	.24*	.24*
PS RT Variability	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	.02	.02	Removed	-	-
Conner Inattention	-.13	-.14	-.13	Removed	-
Conner Hyper/Impulsivity	.28*	.28*	.28*	.19	Removed
Age	-.15	-.15	-.15	-.14	Removed
FSIQ	.02	Removed	-	-	-
PS Velocity (º/s)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	
SCQ	-.13	-.15	-.15	Removed	-
Conner Inattention	-.11	Removed	-	-	-
Conner Hyper/Impulsivity	.26	.19	.20	.15	Removed
Age	-.08	-.06	Removed	-	-
FSIQ	.24*	.26*	.28**	.29**	.23*
PS Amplitude (º)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.15	-.14	-.16	-.18	Removed
Conner Inattention	-.12	-.05	Removed	-	-
Conner Hyper/Impulsivity	.11	Removed	-	-	-
Age	.13	.13	.14	.11	Removed
FSIQ	.12	.11	.13	Removed	-
PS Error Rate (%)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	.22*	.22*	.22*	.22*	Removed
Conner Inattention	-.18	-.17	-.16	-.08	Removed
Conner Hyper/Impulsivity	.10	.10	.11	Removed	-
Age	-.01	Removed	-	-	-
FSIQ	-.05	-.04	Removed	-	-

Note: β coefficients are standardised, *p<0.05, ** p≤0.01

Table 8-4: Beta coefficients from a stepwise linear regression with backward removal predicting Triangle task outcome from ASD and ADHD symptoms, and age for the whole sample

G-D Intentionality	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	.002	Removed	-	-	-
Conner Inattention	.07	.08	.12	.07	Removed
Conner Hyper/Impulsivity	.06	.06	Removed	-	-
Age	.16	.16	.16	.13	.12
FSIQ	.10	.10	.10	Removed	-
G-D Appropriateness	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	.004	Removed	-	-	-
Conner Inattention	.12	.12	.08	Removed	-
Conner Hyper/Impulsivity	-.06	-.06	Removed	-	-
Age	.30**	.30**	.30**	.28**	.28**
FSIQ	.22	.22	.23*	.18	Removed
ToM Intentionality	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.14	-.14	Removed	-	-
Conner Inattention	.30*	.24*	.18	Removed	-
Conner Hyper/Impulsivity	-.08	Removed	-	-	-
Age	.50**	.50**	.48**	.44**	.39**
FSIQ	.26*	.27*	.26*	.17	Removed
ToM Appropriateness	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.13	-.13	Removed	-	
Conner Inattention	.15	.17	.12	Removed	
Conner Hyper/Impulsivity	.04	Removed	-	-	
Age	.45**	.46**	.44**	.42**	
FSIQ	.33**	.32**	.32**	.26**	

Note: β coefficients are standardised, *$p<0.05$, ** $p\leq0.01$

Table 8-5: Beta coefficients from a stepwise linear regression with backward removal predicting Strange Stories task outcome from ASD and ADHD symptoms, and age for the whole sample

Mental State Stories	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.02	Removed	-	-	
Conner Inattention	-.07	-.08	Removed	-	
Conner Hyper/Impulsivity	.09	.09	.03	Removed	
Age	.43**	.43**	.45**	.44**	
FSIQ	.61**	.61**	.64**	.62**	
Physical Stories	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.03	-.03	Removed	-	
Conner Inattention	-.09	-.08	-.09	Removed	
Conner Hyper/Impulsivity	.01	Removed	-	-	
Age	.65**	.65**	.65**	.67**	
FSIQ	.26*	.26*	.26*	.31*	

Note: β coefficients are standardised, *p<0.05, ** p≤0.01

Table 8-6: Beta coefficients from a stepwise linear regression with backward removal predicting Cueing task outcome from ASD and ADHD symptoms, and age for the whole sample

Saccade Latency (mec)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.008	Removed	-	-	-
Conner Inattention	.02	.01	Removed	-	-
Conner Hyper/Impulsivity	.11	.11	.11	Removed	-
Age	-.15	-.15	-.15	-.17	-.19*
FSIQ	.16	.16	.16	.11	Removed
SRT Variability	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.16	-.15	-.15	Removed	-
Conner Inattention	.03	Removed	-	-	-
Conner Hyper/Impulsivity	.20	.22*	.21*	.16	Removed
Age	-.34**	-.35**	-.35**	-.36**	-.35**
FSIQ	.03	.02	Removed	Removed	-
Saccade Amplitude (º)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.13	-.13	-.12	-.13	Removed
Conner Inattention	-.07	-.09	-.11	-.13	Removed
Conner Hyper/Impulsivity	-.03	Removed	-	-	-
Age	.07	.07	Removed	-	-
FSIQ	.09	.09	.06	Removed	-
Anticipatory Saccade (%)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.06	-.06	-.05	Removed	-
Conner Inattention	.08	.05	Removed	-	-
Conner Hyper/Impulsivity	.26	.25	.29**	.27**	.27**
Age	.11	.09	.08	.08	Removed
FSIQ	.06	Removed	-	-	-
Correction Rate (%)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.02	Removed	-	-	-
Conner Inattention	.10	.10	Removed	-	-
Conner Hyper/Impulsivity	-.10	-.10	-.07	Removed	-
Age	.13	.13	.11	.10	Removed
FSIQ	.16	.16	.11	.14	Removed

Note: β coefficients are standardised, *p<0.05, ** p≤0.01

Table 8-7: Beta coefficients from a stepwise linear regression with backward removal predicting Embedded Figure Task outcome from ASD and ADHD symptoms, and age for the whole sample

Accuracy (%)	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.14	-.13	Removed	-	-
Conner Inattention	.05	Removed	-	-	-
Conner Hyper/Impulsivity	.13	.17	.13	Removed	-
Age	.31**	.30**	.30**	.31**	.31**
FSIQ	.15	.15	.16	.16	Removed
EFT False Claim	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.06	-.06	Removed	-	
Conner Inattention	.13	.18	.15	Removed	
Conner Hyper/Impulsivity	.06	Removed	-	-	
Age	-.45**	-.44**	-.44**	-.47	
FSIQ	-.39**	-.39**	-.39**	-.47	
EFT RT to Correct	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	-.13	-.13	-.14	Removed	
Conner Inattention	-.09	-.08	Removed	-	
Conner Hyper/Impulsivity	-.19	-.18	-.24*	-.28*	
Age	-.28**	-.27**	-.27**	-.27**	
FSIQ	-.03	Removed	-	-	

Note: β coefficients are standardised, *p<0.05, ** p≤0.01

Table 8-8: Beta coefficients from a stepwise linear regression with backward removal predicting Block Design task outcome from ASD and ADHD symptoms, and age for the whole sample

BD T- Score	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
SCQ	.13	.13	.12	.12	Removed
Conner Inattention	-.08	-.04	Removed	-	-
Conner Hyper/Impulsivity	.06	Removed	-	-	-
Age	.08	.08	.09	Removed	-
FSIQ	.79**	.79**	.80**	.78	.72**

Note: β coefficients are standardised, *p<0.05, ** p≤0.01

Table 8-9: Beta coefficients from a stepwise linear regression with backward removal predicting Sentence Completion task outcome from ASD and ADHD symptoms, and age for the whole sample

Number of Local Completion	Model 1	Model 2	Model 3	Model 4	Model 5
SCQ	.14	Removed	-	-	-
Conner Inattention	.34*	.39*	.45*	.48**	.30**
Conner Hyper/Impulsivity	-.24	-.24	-.22	-.25	Removed
Age	-.20*	-.19	-.14	Removed	-
FSIQ	-.16	-.17	Removed	-	-

Note: β coefficients are standardised, *$p<0.05$, ** $p\leq0.01$

8.1.6 Discussion

The current chapter adopts a quantitative approach, which assumes that ADHD and ASD are at the extreme end of continuously distributed traits as are the underlying cognitive processes, so that findings from all investigations apply equally to the clinical diagnosis and the extreme end of the ASD-like and ADHD-like traits in the general population (i.e. the control group).

This approach increased the power of the study to further investigate the predictive accuracy of ASD and ADHD traits for different tasks administered in the current study.

For the Go/No-Go task, it was evident that age was affecting all the task performance variables which is in line with previous studies suggesting that neuropsychological performances improves with age due to brain maturation (Happe, et al., 2006; Luna, et al., 2007). Moreover, the response inhibition deficit as measured by the Go/No-Go task was mainly predicted by ADHD traits of inattention and hyperactivity. It was further explored whether inattentiveness or hyperactivity/impulsivity had influence on task performance and was revealed that inattention was the main predictor of RT variability. This finding supports that RT variability is related to fluctuations in attention or maintaining readiness to respond as suggested in ADHD literature (van der Meere, et al., 1996). Moreover, inattention was the main predictor of commission and omission errors; whereas the premature responses were mainly predicted by hyperactivity/impulsivity. In attention research, omission errors are interpreted as difficulties in sustaining attention, whereas commission errors are assumed to reflect a lack of inhibition or impulsivity (Corkum & Siegel, 1993). However, the finding of the current study, suggests premature responding as a more sensitive index of impulsivity than commission errors.

Developmental improvement was observed in voluntary response inhibition as measured by antisaccade task which is in accordance with previous antisaccade research which showed task improvement in older groups (Fischer, Biscaldi, et al., 1997; Klein & Foerster, 2001; Munoz, et al., 2003). It was moreover shown that ADHD traits were affecting antisaccade task

performance. Individuals with more traits of inattention had more variable saccadic responses and also showed difficulties correcting their antisaccade directional errors. This suggests that the observed goal neglect and deficit of response monitoring may be due to not attending the task thoroughly and therefore not recognizing the errors.

In the prosaccade task, it was revealed that the symptoms of inattention and hyperactivity were related to slower and more variable saccadic responses. Social impairments and inattention were associated with smaller saccade amplitude and higher social impairments were associated with higher error rate. However, none of the clinical measures could reliably predict the prosaccade task performance.

Age and cognitive ability appeared to be significant predictors of Triangle Task performance in terms of attributing mental states to triangles and understanding the intended meaning of the animation sequences; and traits of ADHD and ASD were found to have no explanatory roles.

It was revealed that age and inattention were predicting the Strange Stories performance, independent of the story content. The older individuals showed a better understanding and the individuals with more inattentive traits had a poorer understanding. However, when FSIQ was taken into account, the predictive effect of inattention disappeared and it was observed that age and cognitive ability were the main predictors of the task performance.

In the Cueing task, developmental improvement was observed and older individuals showed faster and less variable responses to the cue. Moreover, it was revealed that individuals with more ADHD traits of hyperactivity/impulsivity were more likely to show anticipatory responses.

This finding suggests that anticipatory responding can be considered as a sensitive index of impulsivity.

Accuracy in Embedded Figures Task was found to be influenced by age. This is in line with previous studies that have shown improvement in tasks that require detail-focused processing and an ability to ignore gestalt principles (e.g., EFT) with age (Witkin, et al., 1971). It was revealed that inattentiveness lead to higher number of false claims. However, when taken account of FSIQ, the predictive effect of inattention disappeared and it was observed that age and cognitive ability were the main predictors of the number of false claims. Moreover, it was observed that older individuals and those with higher traits of hyperactivity/impulsivity had superiority in EFT as they were faster in finding the embedded figures. This suggests that being more impulsive was turned out to be advantageous in EFT.

For Block Design task, it was only cognitive ability that predicts the performance and it was revealed that ASD or ADHD traits had no explanatory roles.

It was found that the individuals with more inattention traits showed a greater tendency to make local, globally inappropriate completions to sentences. This may suggest that the observed weak coherence style was mainly due to lack of attention to the sentence context rather than the cognitive style of being more detailed-focused.

8.1.7 Conclusion

The current chapter adopts quantitative approach to investigate the predictive accuracy of ASD and ADHD traits for different tasks administered in the study.

It was revealed that the performance in Go/No-Go task, antisaccade, Cueing task, Embedded Figure Task, and Sentence Completion was mainly associated with ADHD traits. ASD traits had no explanatory roles in the tasks performance.

Age and cognitive ability were the best predictors of performance on the Triangle and Strange Stories Tasks. Block Design task was mainly influenced by cognitive ability.

Chapter 9

Endophenotype

9.1 Chapter Overview

As mentioned in Chapter 1, there has been much interest in recent years in intermediate phenotypes between aetiological risk factors and measurable behaviour/diagnosis, known as 'endophenotypes'. Many studies have focused on neurocognitive features of the disorder in the first-degree relatives of individuals with autism and ADHD in search for endophenotype candidates in these two disorders.

In this chapter, first the definition of the endophenotype and then the literature on candidate endophenotype in ASD and ADHD will be addressed. Subsequently, the cognitive performance of the siblings of the probands (i.e. clinical groups) on selected tasks will be discussed.

9.1.1 Endophenotype

The concept of the endophenotype was first introduced to psychiatry by Gottesman and Shields in 1973 (Gottesman & Shields, 1973). Gottesman proposed several criteria for endophenotypes and indicated that it should be heritable, co-segregate with a psychiatric illness, yet be present even when the disease is not (i.e. state independent), and be found in non-affected family members at a higher rate than in the population (Gottesman & Gould, 2003).

Other researchers have added criteria that require endophenotypes to be part of the causal process by which disease arises (Lavori et al., 2002) or at least be involved in a biologically plausible mechanism of pathogenesis (Castellanos & Tannock, 2002).

Cannon and Keller suggested that endophenotypes 1) should be heritable, 2) should be associated with causes rather than effects of disorders, 3) should vary continuously in the general population, and 4) should optimally be measured across several levels of analysis. They also added that 5) numerous endophenotypes should affect a given complex disorder and 6) endophenotypes that affect multiple disorders should be found for genetically related disorders (Cannon & Keller, 2006).

Kendler and Neale (2010) in a conceptual analysis of endophenotype (EP) noted the two current models for EP: a 'liability-index' and a 'mediational' model (see Figure 9.1). As shown in Figure 9.1a, an EP liability-index (or 'risk indicator') model states that a common set of genes increase risk both for a dichotomous psychiatric disorder (PD) and for a continuous EP. It is in essence a model of pleiotropy in which one set of genetic variants causes variation in both EP and disease risk. Figure 9.1b shows the mediational model for EP, which makes the assumption that the causal pathway from genetic variations to PD passes exclusively through EP (Kendler

& Neale, 2010). In both models, unaffected individuals with high scores on EP would be predicted to be at elevated risk for the development of PD.

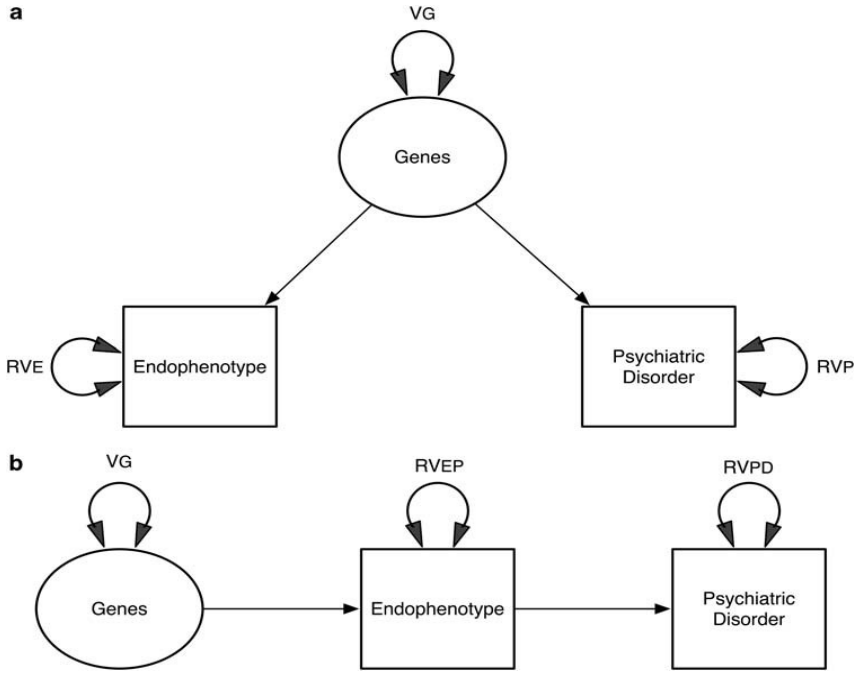


Figure 9-1: Endophenotype Models

(a) A liability-index model for endophenotypes (EPs). Genetic variance (VG) influences both an EP and a psychiatric disorder (PD). These observed variables also have residual variation, RVEP and RVPD, due to other sources. (b) A mediational model for Eps. Genetic variance causes variation in the EP, which in turn causes variation in PD. EP and PD have residual variance components RVEP and RVPD, respectively (Figure from (Kendler & Neale, 2010)).

It is important to note that these models are theoretical models and although the distinction between the two models is conceptually important, it is very difficult to design experiments to discriminate powerfully between the two in human studies.

The 'co-familiality' criterion of EP refers to whether a potential endophenotype is over represented in clinically unaffected relatives of probands compared with controls. This over-representation can be reflected in a significant shift in the mean value for a quantitative trait or in a significant difference in the frequency of a qualitative trait compared with controls (Levy et al., 2008).

Even though unaffected siblings are behaviourally normal, they still possess some of the causal genetic and environmental factors leading up to disorder. Thus, if non-affected siblings show the deficits observed in their affected siblings, then it is feasible that the deficits are caused by a familial risk and as such, form candidate endophenotypes (Gottesman & Gould, 2003)

A number of candidate endophenotypes for ASD and ADHD have been identified in studies done on unaffected relatives of probands. Here, a brief review will be presented.

9.1.1.1 ASD Endophenotypes

As mentioned in Chapter 1, it is well established that ASD is highly heritable and the genetic liability in autism is reflected in behavioural features found in first-degree relatives that are similar but milder to those found in autism which is referred to as the BAP (Wheelwright, et al., 2010).

Many studies have searched for neurocognitive features of the disorder in the first-degree relatives of individuals with autism as neurocognitive characteristics may be more closely linked to underlying brain anomalies and genetic factors than the behavioural phenotype (Hill & Frith, 2003).

Evidence of cognitive biases, similar to weak central coherence, has been claimed to be part of the broader phenotype of autism and has been found in relatives of individuals with ASD. In a study by Baron-Cohen and Hammer (1997), it has been shown that parents of children with autism showed superior performance on EFT, while also being impaired on a task related to theory of mind (the Eyes task) (Baron-Cohen & Hammer, 1997).

In another study by Happé et al. (2001), on a comprehensive assessment of central coherence approximately half of the fathers and a third of the mothers of boys with autism showed consistent WCC across the test battery which was not evident in control groups of parents of boys with dyslexia and boys with typical development. Interestingly, cross-domain coherence was found where weak coherence in the visuo-spatial domain (i.e., fast and accurate performance on the Block Design and EFT) was coupled with weak coherence in the verbal-semantic domain (i.e., completing sentence stems with a local associate that was meaningless to the context). (Happe, et al., 2001)

However, in a recent study by de Jonge et al. (2009), no differences were observed between the parents of individuals with ASD and control parents in BD task and the authors questioned the validity of Block Design reconstruction task as a useful endophenotype (de Jonge, et al., 2009).

Some studies investigated whether EF deficits represent possible endophenotype. For example Wong et al. (2006) investigated parents and non-affected siblings of ASD individuals and controls on a test battery of EF measures including Tower of London, IDED set-shifting task, Response Inhibition and Load (RIL) task, and two tasks assessing generativity (stamp task and Pattern Meanings). They observed that ASD parents showed poorer performance than control parents on a test of ideational fluency or generativity, and ASD fathers demonstrated a weakness in set-shifting to a previously irrelevant dimension. In addition, ASD siblings revealed a mild reduction in ideational fluency and a weakness in non-verbal generativity when compared

with control siblings. Neither ASD parents nor siblings displayed significant difficulties with planning or inhibition. The authors concluded that weaknesses in generativity emerged as stronger potential endophenotypes than planning and cognitive flexibility (Wong, Maybery, Bishop, Maley, & Hallmayer, 2006).

9.1.1.2 ADHD Endophenotypes

ADHD is a strong candidate for endophenotype research, given its high heritability. Several twin and family studies have investigated heritabilities for cognitive processes and the shared heritability/familiality of cognitive measures and ADHD.

Moderate heritability estimates have been reported in twin studies for measures of verbal and spatial working memory (Ando, Ono, & Wright, 2001). A large twin study (400 twin pairs) confirmed moderate heritabilities for MRT, RT variability (as indexed by SD-RT), response inhibition and working memory performance (Kuntsi et al., 2006).

Andreou et al. (2007) assessed RT variability and confirmed the shared familiality between ADHD and SDRT which supports the role of RT variability as an endophenotype mediating the link between genes and ADHD (Andreou, et al., 2007).

In a comprehensive study by Bidwell et al. (2007), 17 measures from main neuropsychological theories of ADHD (*executive function* such as CPT commission errors and omission errors, Set-shifting and working memory; *processing speed*, *arousal regulation* and *motivation/delay aversion* including Delay Aversion Task) were administered. They tested dizygotic (DZ) twin pairs discordant for ADHD and control twin pairs (ages 8–18) and found that individuals with ADHD showed significant impairment on EF, processing speed, and response variability measures compared to controls. Unaffected cotwins of ADHD were also significantly impaired on nearly all the same measures as their ADHD siblings, even when subclinical symptoms of ADHD were controlled. The authors therefore suggested that EF, processing speed, and response variability deficits may be useful endophenotypes for genetic studies of ADHD (Bidwell, Willcutt, Defries, & Pennington, 2007).

Goos et al. (2009) assessed motor response inhibition as a candidate endophenotype. They employed stop-signal task in a group of individuals with ADHD (N=79), their unaffected siblings (N=34), and their biological parents (N=104) in order to test the covariation in inhibitory control within families. They had two control groups: children (N=63) and adults (N=88). They observed that unaffected siblings showed an inhibition deficit intermediate to those of ADHD children and healthy comparison children. Moreover, parents of children with ADHD had a deficit in inhibitory control relative to comparison adults, independent of current symptoms or their history of childhood ADHD. The authors indicated that an inhibitory

control deficit is a cognitive marker of genetic risk shared by parents and offspring (Goos, Crosbie, Payne, & Schachar, 2009).

In a more recent study by Uebel et al. (2010), 205 children with ADHD combined type, 173 nonaffected biological siblings and 53 controls with no known family history of ADHD were examined using a Go/No-Go task. They found that children with ADHD responded more slowly and variably than nonaffected siblings or controls and nonaffected siblings showed intermediate scores for RT variability, false alarms and omission errors under fast and slow event-rates. The authors concluded that RT variability and accuracy parameters could be useful neuropsychological endophenotypes for ADHD (Uebel et al., 2010).

Rommelse et al. in 2008, administered a memory-guided saccade in a group of boys with ADHD (N=14), non-affected siblings (N=18), and 15 control boys aged 7–14 years to assess whether deficits on the memory-saccade task relate to familial factors also causing ADHD. They recorded saccades and found altered oculomotor control in children with ADHD as well as their non-affected siblings compared with controls. Familial deficits were found in accuracy of visuospatial working memory, percentage of anticipatory saccades, and tendency to overshoot saccades relative to controls. The authors concluded that memory-guided saccade deficits may relate to a familial predisposition for ADHD which may be a putative endophenotype (Rommelse et al., 2008).

9.1.2 Summary

A number of candidate endophenotypes for ASD and ADHD have been identified in studies done on unaffected relatives of probands. Superior performance on EFT and BD, impaired ToM, and weaknesses in generativity has been suggested as candidate endophenotype in autism and response variability, processing speed deficits and inhibitory control deficit has been proposed as candidate endophenotype in ADHD.

9.1.3 Aim and Hypotheses

Candidate endophenotypes can be measured at several possible levels, the focus of this PhD is at neurocognitive level.

Given the co-familiality criterion of EP, it was hypothesized that the siblings of the probands would show poorer performance on selected cognitive measures compared to controls.

9.1.4 Participants

15 male, full siblings with IQ≥70 were assessed. None had a clinical diagnosis of ADHD or ASD. This sample includes the siblings from the entire proband dataset including 6 siblings of the comorbid group, 4 from the ASD group and 5 from the ADHD group.

9.1.5 Methods

Selected tasks from the current study which showed case-control differences were chosen as potential endophenotypes. The selected measures were the RT variability, premature responses, and commission errors in Go/No-Go Task; saccade velocity and saccade amplitude as measured by prosaccade; RT variability, saccade velocity and correction rate as measured by antisaccade task; anticipatory saccade and saccade amplitude from Cueing task; and number of local completions from Sentence Completion task.

The main test of shared familial risk (a key criterion for an endophenotype) between a cognitive performance measure and clinical phenotype is a significant difference in cognitive performance between siblings of affected probands and controls (Andreou, et al., 2007). This was tested using independent t-tests.

In case a significant sibling-control difference was observed, probands were also entered in the comparison in order to see whether the mean performance of siblings lie between probands and controls.

9.1.6 Results

9.1.6.1 Demographics

Table 9.1 presents demographic characteristics of the siblings. Comparing siblings with the whole control sample (N=24) showed that the two groups were matched on age ($t_{(37)}$=.07, p>.05). The difference between groups on FSIQ and PIQ was significant ($t_{(37)}$=2.10, p=.04 for FSIQ and $t_{(37)}$=2.29, p=.03 for PIQ). No significant differences was observed on VIQ ($t_{(37)}$=1.44, p>.05).

Table 9-1: Descriptive characteristics of the Sample: Means (SD), [Range]

	Siblings (N=15)	**Controls (N=24)**	***P* value**	**Group Differences**
Age (months) [Range]	125.93 (28.57) [87-184]	126.58 (29.16) [91-180]	.95	
FSIQ [Range]	109.80 (19.78) [78-142]	120.83 (13.06) [102-149]	.04	Controls> Siblings*
WASI PIQ [Range]	104.20 (18.20) [79-140]	115.46 (12.50) [100-141]	.03	Controls> Siblings*
WASI VIQ [Range]	113.53 (19.96) [78-138]	121.71 (15.39) [93-151]	.16	

** Significant at .05 level*

9.1.6.2 Behavioural Profile of the Sample

Siblings and controls were compared to investigate their profile on the screening questionnaires including Conners, SCQ, and SDQ. All of the clinical measures were normally distributed; therefore Independent sample t-test was used.

Table 9.2 shows descriptive statistics for each group on their behavioural profile. No significant differences were observed between siblings and controls on clinical measures (p>.05 for all comparisons).

Table 9-2: Behavioural Profile of the Siblings and Controls: Means (SD)

	Siblings (N=15)	**Controls (N=24)**	***P* value**
SCQ	4.93(4.07)	4.43(3.84)	.71
Conners Inattention	56.29(15.07)	57.83(11.51)	.72
Conners Hyperactivity/ Impulsivity	54.57(12.56)	61.79(17.55)	.17
SDQ Total Score	9.92(6.43)	9.47(5.32)	.84
SDQ Emotion	2.38(2.06)	2.00(2.14)	.63
SDQ Conduct	1.85(1.82)	1.87(1.88)	.98
SDQ Hyperactivity	4.00(2.55)	4.13(2.80)	.90
SDQ Peer	1.69(1.89)	1.47(1.51)	.73
SDQ Prosocial	7.15(2.58)	8.27(1.87)	.20

Table 9.3 demonstrates descriptive statistics (mean and SD) on selected measures of different tasks for siblings and controls. Effect size of the pairwise comparisons (Cohen'd) is also shown in the table.

9.1.6.3 Results from Go/No-Go Task

Data were available from 15 siblings and 19 controls. However, as in the current study the case-control differences were observed between the two groups with ADHD and controls, in order to meet the endophenotype criteria, the siblings of ASD probands were not included in the analysis. Therefore, the analysis carried out included 11 siblings. Initially, analyses were conducted without adjusting for age and IQ. Group differences were explored using Independent sample t-test.

No significant group differences were found for RT variability ($t_{(28)}$=.53, p=.60), premature responses ($t_{(28)}$=.58, p=.57), or commission errors ($t_{(28)}$=.80, p=.43).

9.1.6.4 Result from Antisaccade Task

Data were available from 15 siblings and 22 controls. The mean score of each variable for Gap/Step/Overlap conditions was calculated and group differences were explored using Independent sample t-test. Initially, analyses were conducted without adjusting for age and FSIQ.

No group differences were observed for the number of correct trials in antisaccade ($t_{(35)}$=.40, p>.05) with the mean and SD as follows: control: mean=28.68 (14.80); Siblings: mean=26.73 (14.54), indicating that siblings, like the control group, appeared to be willing and able to perform this task.

No significant group differences were found for RT variability ($t_{(31)}$=-1.20, p=.24) and peak velocity ($t_{(33)}$=.30, p=.77). A significant difference was observed between siblings and controls in correction rate ($t_{(30)}$=2.64, p=.01) reflecting a significantly lower rate of correction in siblings. A medium effect sizes was detected for RT variability and a large effect size was found for correction rate comparisons.

As there was a significant sibling-control difference for correction rate, probands were also entered in the comparison. ANOVA was run with group as the between-subjects factor and revealed a significant difference between groups ($F_{(2,117)}$=4.33, p=.01, η^2=0.069). As the sample sizes were very different (probands: N=88), Hochberg's GT2 was used which showed a significantly higher rate of correction rate in controls than siblings (p=.04) and probands (p=.02). No significant differences was detected between probands and siblings (p=.94). Figure 9.2 shows the mean of the correction rate in each group.

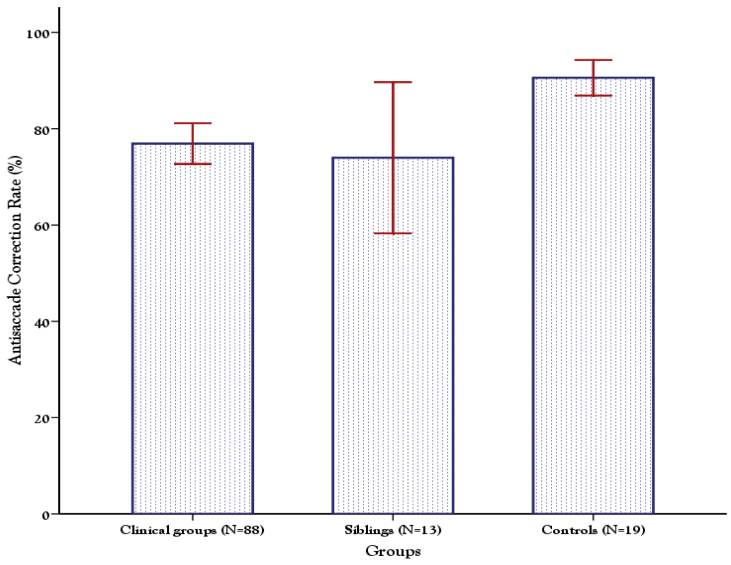


Figure 9-2: Antisaccade Correction Rate (%) by groups

9.1.6.5 Result from Prosaccade Task

Data were available from 15 siblings and 22 controls. The mean score of each variable for Gap/Step/Overlap conditions was calculated and group differences were explored using independent sample t-test. Initially, analyses were conducted without adjusting for age and IQ.

A significant group differences were observed for the number of correct trials in prosaccade ($t_{(35)}$=2.40, p=.02) with the mean and SD as follows: control: mean=49.68 (5.57); Siblings: mean=44.27 (8.21) indicating a better performance in the control group.

No significant group differences were found for peak velocity ($t_{(35)}$=.17, p=.87). A non-significant trend was observed for amplitude ($t_{(35)}$=1.89, p=.07), reflecting smaller amplitudes in siblings. However, as it is shown in Table 9.3 a large effect size was detected for amplitude with a limited power for a .05 two-sided level of significance (power=.47).

9.1.6.6 Result from Cueing Task

Data were available from 13 siblings and 22 controls. The mean score of each variable for different cue type and congruency was calculated and group differences were explored using independent sample t-test. Initially, analyses were conducted without adjusting for age and IQ.

As in the current study the case-control differences in percentage of anticipatory saccade was observed between the two groups with ADHD and controls, in order to meet the endophenotype criteria, the siblings of ASD probands were not included in the analysis. Therefore, the analysis carried out included 9 siblings. However, for amplitude, all the siblings were included (N=13).

No significant group differences were found for percentage of anticipatory saccade ($t_{(29)}$=.45, p=.65) and a significant group differences were observed for amplitude ($t_{(33)}$=2.08, p=.04) with the control group showing bigger amplitude than siblings. As it is shown in Table 9.3 a large effect size was detected for the latter comparison.

As there was a significant sibling-control difference for amplitude, probands were also entered in the comparison. ANOVA was run with group as the between-subjects factor and revealed a significant difference between groups ($F_{(2,121)}$=4.61, p=.01, η^2=0.071). As the sample sizes were very different (probands: N=89), Hochberg's GT2 was used which showed a significantly bigger amplitude in controls than siblings (p=.04) and probands (p=.01). No significant differences was detected between probands and siblings (p=.93).

9.1.6.7 Result from Sentence Completion Task

Data were available from 15 siblings and 20 controls. Initially, analyses were conducted without adjusting for age and IQ. Group differences were explored using Independent sample t-test.

A non-significant trend was observed in the number of local completions ($t_{(33)}$=1.80, p=.08) with the siblings showed a greater tendency to make local, globally inappropriate completions to sentences. As it is shown in Table 9.3 a medium effect size was detected for number of local completion with a limited power for a .05 two-sided level of significance (power=.37).

Table 9-3: Siblings-Controls comparisons on different task measure: Means (SD)

		Siblings	Controls	Cohen's d (Cont.-Sibs)	*P* value
Go/No-Go	**RT Variability***	109.07 (40.56)	120.47 (63.37)	.21	.60
	Premature Responses*	1.72 (2.42)	2.85 (4.72)	.30	.57
	Commission Errors (%)*	36.00 (12.96)	40.74 (16.95)	.31	.43
Antisaccade	**RT Variability**	77.41 (22.65)	68.17 (20.89)	-.42	.24
	Velocity (º/s)	373.03 (67.74)	379.80 (66.56)	.10	.77
	Correction Rate (%)	73.98 (25.99)	90.59 (7.68)	.87	**.01**
Prosaccade	**Velocity (º/s)**	399.52 (56.03)	403.03 (65.29)	.06	.87
	Amplitude (º)	13.40 (1.04)	14.06 (1.05)	.63	**.07**
Cueing Task	**Anticipatory Saccade (%)***	9.71(7.64)	11.62 (11.53)	.19	.65
	Saccade Amplitude (º)	13.66 (.85)	14.32 (.95)	.73	**.04**
SC	**Number of Local Completion**	1.13 (1.51)	.45 (.69)	-.58	**.08**

** For these measures only the siblings of the two groups with ADHD were included in analysis.*

SC=Sentence Completion

All the above analyses for group comparisons on different measures of different tasks were repeated and the effect of age and IQ was controlled this time using age and FSIQ as covariates. When adjusted for age, and then separately for FSIQ the findings did not substantially differ from the unadjusted analyses. Finally, all the analyses were repeated with both age and FSIQ entered as covariates. Again, no differences from unadjusted analyses were observed (As the findings did not change after controlling for age and FSIQ, in order not to be repetitive, the statistics were not reported).

9.1.7 Discussion

Two conceptual models of endophenotype have been suggested by Kendler and Neale (2010): 1) a 'liability-index' which is a model of pleiotropy in which one set of genetic variants causes variation in both EP and disease risk and; b) a 'mediational' model which makes the assumption that the causal pathway from genetic variations to PD passes exclusively through EP. In both models, unaffected individuals with high scores on EP would be predicted to be at elevated risk

for the development of PD (Kendler & Neale, 2010). The mediational model implies that targeting the EP in unaffected individuals would likely reduce the risk of the PD, whereas in the liability index model, the EP and PD are independent.

These models are theoretical and it is very difficult to design experiments to discriminate between the two in human studies. One way to test these models is by assessing the effect of treatment on EP and PD. Another approach would be where specific genetic marker is found to be associated with EP and/or PD.

It should be noted that the current study design was not a suitable design to test the two models and favour one of the models.

Many studies have searched for neurocognitive features of ASD and ADHD in their first-degree relatives as neurocognitive characteristics may be more closely linked to underlying brain abnormalities and genetic factors than the behavioural phenotype.

A number of candidate endophenotypes for ASD and ADHD have been identified in previous studies. Superior performance on EFT and BD, impaired ToM, and weaknesses in generativity has been suggested as candidate endophenotype in autism (Baron-Cohen & Hammer, 1997; Happe, et al., 2001) and response variability, processing speed deficits and inhibitory control deficit has been proposed as candidate endophenotype in ADHD (Andreou, et al., 2007; Bidwell, et al., 2007; Goos, et al., 2009; Uebel, et al., 2010).

This study had the chance to look at the cognitive profile of a small number of siblings of ADHD and ASD probands, with no clinical diagnosis of ADHD or ASD on selected measures from the current study, in order to search for potential endophenotypes for a broad neurodevelopmental phenotype.

Some aspects of executive functioning such as neuropsychological parameters of sustained attention and response control in a Go/No-Go task and response inhibition and monitoring in an antisaccade task were explored. Moreover, visual attention at a basic level in a prosaccade task was assessed. Of the tasks assessing Theory of Mind and social cognition, selected measures of Cueing task were chosen, and from tasks assessing Central Coherence, Embedded Figures Task and Sentence Completion were selected.

For the Go/NO-Go task the siblings of the ADHD and comorbid groups were included in the analysis, because case-control association with performance measures from this task were only found in the two groups with ADHD. In spite of group differences between the two groups with ADHD and control group in RT variability, premature responses, and commission errors; no differences were observed between siblings and controls on these measures. Furthermore effect sizes were small and controls showed poorer performance on the task parameters. However, this would not necessary indicate that theses measures are not suitable

endophenotypes as the sample size of the current study was small and this would preclude any conclusion like this.

Performance on antisaccade task is one of several candidate endophenotypes for schizophrenia and poor performance on antisaccade task has been reported in clinically unaffected relatives of schizophrenics (Levy, et al., 2008); however, no study has searched whether eye tracking dysfunction can be a potential endophenotype in ADHD and ASD.

In the current study as was reported in Chapter 5, the largest effect size was observed for the antisaccade correction rate for the comparisons of the three clinical groups and controls. Interestingly, the same pattern was observed in the comparison between siblings and controls. The siblings of probands with a diagnosis of ASD, ADHD and comorbid ASD-ADHD failed to correct a significant proportion of their direction errors compared to controls. This suggests the same deficit in response monitoring and goal neglect (and possibly not recognizing the errors) in the siblings of the three clinical groups to that observed in the probands. The antisaccade correction rates therefore meet the co-familiality criterion for a broad endophenotype that is shared across the neurodevelopmental disorders of ASD and ADHD.

Saccade amplitude seemed to be a suggestive endophenotype as in prosaccade task, a non-significant trend, and in Cueing task a significant difference was observed between siblings and controls. It was evident that the siblings of the three clinical groups could produce saccades, however smaller compared with controls. This was the similar to the findings of the probands as was discussed in Chapter 5 and Chapter 6 for prosaccade and Cueing task, respectively.

For the anticipatory saccade as measured by Cueing task, siblings of the ADHD and comorbid groups were included in the analysis, because case-control association with performance measures from these tasks were only found in the two groups with ADHD. Although significant differences between the two groups with ADHD and control group were observed; no differences were found between siblings and controls on these measures. Controls showed higher rate of anticipatory saccades compared with siblings with small effect sizes of the comparisons. However, this would not necessary indicate that this measure is not a suitable endophenotype as the sample size of the current study was small and this would preclude any conclusion like this.

The siblings of the probands with a diagnosis of ASD, ADHD and comorbid ASD-ADHD showed a greater tendency to complete sentences with local, context inappropriate responses compared with controls. A medium effect size of the pairwise comparison with a limited power therefore suggests that the number of local completions can be considered as a candidate for a broad endophenotype that is shared across the neurodevelopmental disorders of ASD and ADHD.

9.1.8 Conclusion

The current study had a chance to look at the performance of the siblings with no clinical diagnosis of ADHD or ASD on selected measures from the current study which showed case-control differences, in order to search for potential endophenotypes.

Even though the sample size of the siblings was very small, it was revealed that antisaccade correction rate and saccade amplitude meet the co-familiality criterion for a broad endophenotype that is shared across the neurodevelopmental disorders of ASD and ADHD.

Moreover, the finding of number of local completion in Sentence Completion task was promising and suggests that it can be considered as a candidate for a broad endophenotype.

Even though unaffected siblings were behaviourally normal, they still showed some of the deficits observed in their affected probands and significant shift in the mean value for some of the quantitative traits compared with controls. This finding would suggest that the deficits are caused by a familial risk and the unaffected siblings might possess some of the causal genetic and environmental factors leading up to disorder.

9.1.9 Limitations and Suggestions for Future Research

The present study had a number of limitations. First, the sample size of the siblings was very small and the sibling group consisted of a heterogonous group consisting of three categories of neurodevelopmental disorders (ADHD, ASD and the comorbid ASD-ADHD group). This meant that this sample had most power to identify endophenotypes that are in common between the neurodevelopmental disorders, ASD and ADHD. The small sample size and heterogeneity, however, limits the extent to which the findings can be interpreted and generalised.

It is suggested that future studies focus on larger samples looking for candidate endophenotype for each disorder separately, as well as those that span across disorders. Moreover, previous studies have not investigated saccadic eye movements, although the data presented here indicate that the antisaccade correction rate which taps cognitive processes such as response monitoring shows promise for future studies of endophenotypes that might span across disorders. This is potentially interesting since we know that around half of the genetic influences are shared between the two disorders, and this might be reflected in processes that are shared between ADHD and ASD.

Chapter 10

Final Discussion

10.1 Chapter Overview

This chapter attempts to integrate the findings of this thesis and place them into the context of previous research. The research proposal and the aims of the current investigations will first be reviewed. Then, the strengths and the limitations of the research, followed by the key findings and the implications of the findings, and suggestions for the directions of future research will be discussed.

10.2 Introduction

ASD and ADHD are both defined on the basis of behavioural impairments and there is no informative biological test available for the diagnosis of these two child neurodevelopmental disorders yet. Considering the heterogeneous profiles of ADHD and ASD, it is important to ascertain a good phenotypic definition for aetiological investigations; this consequently would affect the accuracy of estimates of prevalence rates of the disorders.

The main aim of the current study was to investigate whether ASD and ADHD could be discriminated based on their neuropsychological profiles and whether any overlap in the pattern of cognitive impairment exists between the two disorders. Moreover, the study aimed to explore whether the cognitive profile of the comorbid ASD-ADHD group resembles the profile of either pure group or a pattern representing both disorders. Finally, the thesis intended to test whether cognitive biomarkers may represent a putative endophenotype.

The current study attempted to achieve this by administering an extensive task battery, tapping the three influential cognitive accounts of ASD and/or ADHD, including Executive Function (EF), Theory of Mind (ToM) and social cognition, and Weak Central Coherence (WCC) accounts in boys in the age range of 7 to 16 years with FSIQ $\geq$ 70. In total, 135 boys were assessed in this study in five subgroups including 35 individuals with a research diagnosis of ADHD, 19 individuals with a research diagnosis of ASD, 42 in a comorbid group, 24 controls and 15 siblings.

10.3 Strengths of the Study

The current study has extended the previous studies and made contributions to ASD and ADHD literature by administering an extensive test battery in five different groups of participants. The strengths of the study were as follow:

First, by making direct comparisons of ASD and ADHD groups: There are only a few studies that have directly compared neuropsychological profiles of children and adolescents with a diagnosis of ASD and ADHD in relation to different cognitive accounts in order to map their shared cognitive overlaps and differentiations. This was the first to compare the cognitive profile of individuals with ASD or ADHD on such an extensive test battery assessing three influential cognitive accounts.

Second, by considering the comorbidity: Studies focusing on cognitive profiles of individuals with a comorbid ASD-ADHD diagnosis are sparse. Most of the previous studies have not acknowledged the co-occurrence of the two disorders while assessing the performance of the diagnostic groups. Moreover, even when comorbidity was recognised as an issue, there was a tendency to exclude children and adolescents with a comorbid diagnosis in order to study the pure picture of the disorders. These decisions have led to a gap in our knowledge of the cognitive profile in the comorbid cases. The current study attempted to fill the gap by exploring the performance of individuals with a comorbid ASD-ADHD diagnosis compared to the pure groups. The fact that a significant proportion of cases were reassigned from clinical diagnostic groups to research diagnostic groups, especially with respect to undiagnosed comorbid cases, suggests that the findings from this study are maybe more representative than the previous research.

Third, by implementing rigorous diagnostic assessment with state-of-the-art instruments and stringent group allocation: The study applied rather tight inclusion/exclusion criteria to define the diagnostic groups in order to reduce the number of confounds.

Fourth, by using novel measures and approaches: In addition to collecting data on motor reaction time across different tasks, the study benefited from using the Eye Tracker which was able to provide direct information, not confounded by the motor ability of the individuals. This was the first study to look at prosaccades and antisaccades using a Gap/Overlap paradigm comparing the groups with ASD and/or ADHD. Moreover, this study for the first time compared the attentional orienting in an ASD group with ADHD and comorbid groups by using a cueing paradigm which measured saccadic reaction time (SRT).

Fifth, by adopting a quantitative approach: In addition to a categorical approach, a quantitative/dimensional approach was adopted in order to further investigate the predictive accuracy of ASD and ADHD traits for different tasks administered in this study.

Sixth, by looking for a candidate endophenotype: This study had the chance to assess the cognitive profile of a group of siblings of ADHD and ASD probands, with no clinical diagnosis of ADHD or ASD in order to search for potential endophenotypes for a broad neurodevelopmental phenotype.

10.4 Limitations of the Study

The present study had a number of limitations.

10.4.1 Sample Size

Due to the strict inclusion and exclusion criteria employed in the current study, the sample size of the groups, although comparable to previous studies on most of the tasks, was relatively small and unequal across groups. The investigation started with a relatively similar number of individuals with a clinical diagnosis of ASD (N=35) and ADHD (N=40). However, further group reallocation based on the research criteria reduced the sample sizes of the pure groups, in particular the ASD group, and therefore reduced the power of the study to find between group differences. This would in return increase the likelihood of Type II errors when addressing research questions.

The sample size of the siblings was also limited, and consisted of a heterogonous mix of the siblings from the three categories of neurodevelopmental disorders (ADHD, ASD and the comorbid ASD-ADHD group). The small sample size and heterogeneity, therefore, limits the extent to which the findings on a putative endophenotype can be interpreted and generalised.

10.4.2 Sampling Bias

The sampling was not random and from all the potential cases identified in the clinics based on the inclusion/exclusion criteria, only 48% participated in the study. Therefore, the results are based on a small selected clinic samples and subject to sampling bias. This would therefore limit the generalisability of the results of the current study.

Ideally, to obtain a representative sample, the general population should be screened and cases should be recruited from the general population. This was nor feasible in the current investigation and recruitment had to be through established clinics. It was also not possible within the time frame of the study to recruit consecutive series of cases from clinics. Consequently, sampling bias may exist but the extent of it is unknown.

Regarding the sampling source, the main sources of recruitment were the neurodevelopmental clinics which had similar pattern of referrals, and only a few individuals were recruited from other sources (NAS website) (Please see Table 4-1). Therefore, ascertainment bias is unlikely to have an influence on the results of the study.

As discussed in Chapter 2, both the referral factors and the non-random sampling were believed to have an effect on the picture of comorbidity observed in the current study. All the outpatient clinics in different boroughs where the recruitment of participants took place were secondary referral clinics which were expected to have a higher rate of comorbidity compared with the general population (Berkson effect). This is because of the fact that individuals with more than

one disorder are more likely to be referred and be part of a clinical sample. Moreover, as the current clinical sample did not consist of a random sample of those who meet criteria within the population, it is more likely that the individuals with a greater number and severity of symptoms would be more likely to receive treatment and thus be part of an enriched sample.

Recruitment of healthy controls may also be subject to sampling biases. For example, parents may have been more likely to involve their son in the current study if they suspected they had potential ADHD/ASD related symptoms. Although none of the control individuals scored above the threshold for ASD traits, several scored above the threshold on the Conners screening questionnaire for ADHD traits. However, only one individual was excluded due to the presence of clinically significant ADHD traits.

10.4.3 The effect of age

The age range of the participants was quite wide. Even though no group differences for age were found, this would further increase the variability of the responses and limit the interpretation of the findings. This variability could be taken into account by reporting the analysis with and without covarying for age.

10.4.4 The effect of IQ

It was not possible to match groups exactly on IQ distribution which may have confounded the findings. Although this variability could be taken into account by covariation, it may still limit some conclusions made regarding the group effect. Moreover, there are some debates in using IQ as a covariate in analyses in psychopathology research. For example, some have suggested acknowledging IQ as a feature of disorder rather than a confound (Miller & Chapman, 2001); thereby removing the effects of IQ may essentially remove some of the effects of group differences attributed to having a diagnosis. Therefore, it was decided to report the findings of the current study with and without covarying for IQ.

10.4.5 The Control group

A further limitation of the current study was the characteristics of the control group as 14 of them scored above the cut-off on either domain or both domains of the Conners scale. Even though PACS was then administered in this subgroup to ensure that they did not meet the diagnostic criteria for ADHD, it questions the purity of individuals within the control group and it is still possible that the relatively poor performance of the control group in the current study might be partly due to their ADHD traits that had an unfavourable influence on their task performance.

10.4.6 Generalisability of the study

The challenge of heterogeneity is common in ASD and ADHD research. The present study was undertaken in children and adolescents with HFA and Asperger's Syndrome with high verbal

abilities. Therefore, the results deriving from this study cannot be generalised to ASD populations with below average verbal abilities. Moreover, the participants had a diagnosis of combined-type ADHD, therefore, the findings from this study can only be generalised to children and adolescents with combined type ADHD and not other subtypes.

10.4.7 The Test Battery

The tasks administered for the purpose of this thesis were embedded in a larger test battery and the tasks were presented in a fixed order. Therefore, the effect of fatigue, especially on the tasks administered more towards the end of each order set was inevitable. However, this would likely affect all the individuals independent of their group allocation. Moreover, in order to minimise the effect of fatigue, several breaks were given to the participants and tasks alternated between pencil-and-paper and computer-administered, as well as between visual and verbal modalities.

For the convenience of the participants and due to test demands, families were given the option to spread the assessment over two separate sessions or to carry out testing in one day. This different task administration might be a confound as it may have influenced on the task performance; however, the study attempted to minimise the confounding effect of task administration by introducing a long break in the middle of the one-day assessments. Moreover, the option was given to all participants, regardless of their group allocation.

10.4.8 Statistical Analyses

There is a trade-off for controlling the family-wise error: if a test is conservative (the probability of Type I error is small), then it is likely to increase the risk of missing the genuine difference between the groups (the probability of Type II error will be high).

In the current sample, the relatively small sample size and uneven group numbers may have increased the likelihood of Type II error. Moreover, as some of the analyses were exploratory, the statistics used in the study were biased towards the Type II error.

Some protection against Type I error was provided by the use of ANOVA in analysis. LSD post -hoc was employed to examine between-group differences; which makes no attempt to control the Type I error and does not control for the family-wise error.

As this study is one of the only studies which has explored cognitive markers for ASD, ADHD, and a comorbid group, it was considered best to present findings uncorrected for multiple testing so that future research can further test the cognitive traits that may represent markers. Therefore, an alpha adjustment (Bonferroni correction for multiple comparisons) has not been applied systematically throughout the thesis in order to avoid Type-II errors. Nevertheless, the results reported here need to take into consideration the fact that there was multiple testing.

10.5 Key Findings and the Implications of Findings

The findings of each task were discussed thoroughly in the relevant chapters. Here, a summary of key findings is provided.

10.5.1 The Co-occurrence of the Two Disorders

With rigorous, in-depth diagnostic assessments, the study demonstrated that there are individuals who meet criteria for both disorders. It was revealed that in addition to individuals who were assigned a diagnosis of comorbid ASD-ADHD from the clinics, of the whole sample of individuals with a clinical diagnosis of HFA/ Asperger's disorder recruited in the study, 17 individuals were reassigned to a comorbid group, and from those with a clinical diagnosis of combined type ADHD, 5 were further classified in the comorbid group. These reallocations doubled the number of individuals in the comorbid group.

Moreover, the ADHD characteristics in the comorbid group were similar to the pure ADHD group. A similar distribution of subtypes (inattentive, hyperactive/impulsive, or combined) was observed in ADHD in the presence of ASD, similar to the profile of the pure ADHD group.

Even though these data may not fully represent the pattern of comorbidity from population derived samples, it highlights the importance of considering the co-occurrence of the two disorders, both in clinical and research settings, as it has been underestimated. This finding is in keeping with previous studies which have reported the co-occurrence of the two disorders and which have therefore questioned the rational for excluding a comorbid diagnosis of ADHD and ASD (Goldstein & Schwebach, 2004; Reiersen & Todd, 2008).

10.5.2 Cognitive Profiles in each Group and the Contribution of the Study to Existing Knowledge

In some instances, the cognitive findings were consistent with the expectations; however, some notable differences from previous observations were found. The differences in findings could be partly due to different methodology or sample characteristics. A more concerning explanation could be that previous studies have not evaluated their ASD group for ADHD symptomatology and vice versa. This could consequently confound their findings as it is not clear to what extent their findings are due to overlooked comorbidity. However, it should be noted that due to limited power of the current study, the findings should be interpreted with caution.

Some of the cognitive measures appeared to have evaluated the cognitive functions which are unique to a disorder and which may represent distinctive aetiological pathways. However, the other measures tapped into the shared cognitive correlates of ASD and ADHD which may conversely suggest similar aetiological pathways.

10.5.2.1 Cognitive Findings in ASD Group Compared to Control Group

The response inhibition deficit reported in previous studies in the ASD group using the Go/No-Go task (Geurts, et al., 2004; Happe, et al., 2006; Ozonoff & Jensen, 1999) was not replicated in the current study. One explanation could be that the previous studies have not evaluated their ASD group for ADHD symptomatology which could have biased their findings.

Prosaccade tasks revealed that the ASD group was able to initiate saccadic eye movements at a comparable level to the control group and no impairment in engagement and disengagement of visual attention was found. However, it was evident that individuals with ASD were making saccades with smaller amplitude and reduced peak velocity compared to controls. Moreover, it was shown that as autistic symptoms increased, the amplitude became smaller.

Contrary to expectations based on previous research in ASD group that found an increased rate of antisaccade errors (i.e. a failure to suppress the prepotent prosaccade) (Goldberg, et al., 2002; Luna, et al., 2007; Minshew, et al., 1999), the ASD group did not show higher directional errors; however, they corrected less errors relative to controls which is indicative of an impairment in response monitoring. This finding replicates previous studies which indicated that control participants typically correct most of their errors in antisaccade task; however, certain clinical groups such as ASD fail to do so (Goldberg, et al., 2002; Luna, et al., 2007; Minshew, et al., 1999).

Findings from the Triangle Task differed from current literature suggesting ToM deficits in individuals with ASD (Abell, et al., 2000; Castelli, et al., 2002; Salter, et al., 2008). The ASD group showed competence both in terms of attributing mental states to animations and in accuracy of mental state descriptions. Symptoms of autism, in particular communication difficulties and restricted, repetitive interests and behaviours, were related to less accurate descriptions in animations with mental state contents which reflected the difficulties children with ASD have in understanding social situations. However, they performed the task at the level of age-matched controls which may suggest that they are able to apply compensatory mechanisms such as high cognitive and verbal abilities which help them in structured and verbally mediated situations.

In the Strange Stories task, the ASD group showed a tendency for poorer understanding of mental stories. This finding is in line with the studies that suggested Strange Stories task is a sensitive means of testing advanced mentalising ability in children with HFA (Brent, et al., 2004; Kaland, et al., 2005; White, et al., 2009). Moreover, it was revealed that greater symptoms of ASD (i.e. social and communication impairments) were related to greater difficulty in understanding stories independent of the content. However, it is important to note that the relatively poorer performance of the ASD group was mainly mediated by the difference in the verbal ability as the difference disappeared when VIQ was controlled for.

Contrary to expectations, no evidence for deficits in attentional orienting to social stimuli was found in the ASD group and they did not differ in their responses to different cue types (i.e. eye gaze and arrow) from controls. This is in line with studies that reported the same pattern of response in controls and ASD groups (Ames & Jarrold, 2007; Kuhn, et al., 2010; Kylliainen & Hietanen, 2004; Pruett, et al., 2011; Swettenham, et al., 2003), but contrasts with those that found a greater salience to social cues in the control group than ASD group (Chawarska, et al., 2003; Ristic, et al., 2005; Senju, et al., 2004).

In contrast to the current view of WCC style in visuospatial domain as measured by EFT (Jolliffe & Baron-Cohen, 1997; Ropar & Mitchell, 2001; Shah & Frith, 1983; van Lang, Bouma, et al., 2006) and BD task (Happe, 1994b; Pellicano, et al., 2006; Ropar & Mitchell, 2001; Shah & Frith, 1993), the weak drive for central coherence in individuals with ASD was not confirmed in the present study. However, a disregard for sentence context and a WCC style in verbal domain was observed in individuals with ASD in the Sentence Completion Task in line with previous studies (Booth & Happe, 2010). Moreover, it was found that inattention and restricted, repetitive interests and behaviours were related to the tendency to produce more local completions.

10.5.2.2 Cognitive Findings in ADHD Group Compared to Control Group

The ADHD group showed deficits in response selection/inhibition on the Go/No-Go task which is in line with ADHD literature suggesting impaired inhibitory control as one of the main difficulties in individuals with ADHD (Barkley, 1997, 1998; Iaboni, et al., 1995; Rubia, Smith, & Taylor, 2007; Rubia, Taylor, et al., 2001). The poor inhibitory response was found in a higher rate of commission errors and premature responses, demonstrating a difficulty in the inhibition of prepotent responses. Moreover, consistent to the hypotheses, ADHD symptoms were associated with EF deficits, which would suggest that the observed impairment in the ADHD group was partly due to their inattentiveness and hyperactivity/impulsivity.

Prosaccade tasks revealed that ADHD group were able to initiate saccadic eye movements at a comparable level to the control group. No impairment in engagement or disengagement of visual attention was found in this group. However, it was evident that the individuals with ADHD were making saccades with smaller amplitude and reduced peak velocity compared to controls. Moreover, it was shown that as ADHD symptoms increased, the amplitude became smaller.

The studies that found an elevated number of antisaccade errors are in the majority (Mostofsky, Lasker, Cutting, et al., 2001; Munoz, et al., 2003)(Klein, et al., 2003)(O'Driscoll et al., 2005) indicating that children with ADHD are less able than controls to suppress inappropriate oculomotor responses. This finding was not replicated in the present ADHD group; however, they corrected less error relative to controls which is indicative of impairment in response

monitoring. This finding replicates previous studies which showed that control participants typically correct most of their errors in antisaccade task; however, certain clinical groups such as ADHD fail to do so (Karatekin, et al., 2010; Klein, et al., 2003; Mostofsky, Lasker, Singer, et al., 2001; Munoz, et al., 2003; O'Driscoll, et al., 2005).

In line with previous studies by Karatekin et al. (Karatekin, 2006; Karatekin, et al., 2010), greater variability of saccadic RTs in the ADHD group was evident during antisaccades, suggesting attentional fluctuation in individuals with ADHD.

Individuals with ADHD were found to be able to pass the Triangle Task. Their performance was shown to be related to their inattention and hyperactivity/impulsivity symptoms which have had an unfavourable effect; however, in this set of short cartoons, individuals with ADHD could perform the task at the level of age-matched controls.

The ADHD group showed poorer performance in mental state stories compared to controls, which is in contrast to the findings of Charman et al. (2001) that showed intact performance of individuals with ADHD in the Strange Stories task (Charman, et al., 2001) but which supports the studies that found mentalising difficulties in ADHD groups (Buitelaar, van der Wees, et al., 1999). Moreover, it was revealed that symptoms of hyperactivity were associated with poorer performance in mental state stories. However, it is important to note that the difference between ADHD and controls seems to be driven by the lower verbal ability in this group as the difference disappeared after controlling for VIQ.

In the Cueing task, the ADHD group showed the same pattern of response to different cue types as the control group: they were slightly faster in the arrow trials than the gaze trials and they showed the cueing effect only to the arrow and not to gaze cues. However, the ADHD group showed a higher rate of anticipatory saccade than the control group.

In the EFT, the ADHD group was faster in finding the embedded figures than controls, even though the difference did not reach significance. In addition, they showed a higher rate of false claims. It was also revealed that being more impulsive appeared to be advantageous in the ADHD group as they could find the embedded figures faster.

In the Sentence Completion Task, the ADHD group showed a detail-focused style of performance which was associated with symptoms of inattention and hyperactivity/impulsivity. This suggests that the higher number of local completions in the Sentence Completion Task may reflect a lack of attention to the sentence context.

10.5.2.3 Cognitive Findings in Comorbid ASD-ADHD Group

Comorbidity did not necessarily lead to more severe impairment than in the pure groups. In summary, it was found that in the comorbid ASD-ADHD group, the cognitive task performance was in some instances (e.g. response inhibition) similar to the ADHD group, and

in other instances (e.g. understanding the stories with social contents) similar to the ASD group, and finally for some measures (e.g. response monitoring and a weak coherence style in the verbal domain), their performance was similar to both groups.

There were not any instances in which the comorbid group showed a pattern of impairment that was unique to them.

10.5.2.3.1 Similarities in Performance to ADHD group

In the Go/No-Go task, a similar style of premature responding with a high rate of commission errors to those found in the ADHD group was observed in the comorbid group. This may suggest that the neuropsychological correlate of ADHD in the presence of ASD is similar to ADHD on its own. In this group, both ADHD and autistic symptoms were associated with the poor inhibitory control, which would therefore suggest that their executive control is related to inattentiveness, and hyperactivity/impulsivity, as well as social and communication difficulties.

Similar to the ADHD group, greater variability of saccadic RTs was observed in comorbid group during antisaccades.

The performance of the comorbid group was similar to the ADHD group in EFT and they were relatively faster than controls and the ASD group in finding the embedded figures. They also showed a higher rate of false claims.

10.5.2.3.2 Similarities in Performance to ASD Group

In the Strange Stories task, they showed a similar pattern of performance to the ASD group, relatively poorer understanding of mental state stories than controls, which again appeared to be mediated by differences in VIQ.

10.5.2.3.3 Similarities in Performance to both Groups

Similar to both ASD and ADHD groups, individuals with a comorbid diagnosis were able to initiate saccadic eye movements in the prosaccade task. No impairments in engagement or disengagement of visual attention were found in this group. However, it was evident that they were making saccades with smaller amplitudes compared with controls.

In the antisaccade task, they failed to correct a significant proportion of their directional errors and showed the same response monitoring deficit as was observed in ASD and ADHD individuals.

Similar to the ASD and ADHD groups, individuals with a comorbid diagnosis could attribute mental states to triangle animations. They also exhibited a similar performance in the Sentence Completion task by showing a tendency for local completions.

10.5.2.4 Tasks Differentiating the Two Pure Groups

Some of the measures showed sensitivity to differentiate the two groups of ADHD and ASD. These measures should be incorporated into future research of candidate biomarkers.

Poor inhibitory control appeared to serve as a useful candidate biomarker as deficits in response inhibition were more pronounced in the ADHD group.

This was the first study to compare the EFT performance in ASD and ADHD groups. The findings of the EFT in ADHD and ASD groups were contrary to expectations. On the basis of the WCC account, the superior performance of the ASD group both in terms of RT and accuracy was expected. However, it was revealed that the ADHD group outperformed the ASD and control groups in RT and showed the same level of accuracy. This finding queries the validity of the EFT as a task measuring the detail-focused style of individuals with ASD. Moreover, it queries the specificity of the WCC account to ASD and further suggests that the EFT should be revisited in future studies.

10.5.2.5 Tasks Showing Similarities of the Two Pure Groups

It was observed that the performance of the ADHD and ASD groups were to a large extent similar in some of the cognitive tasks, possibly in favour of a common cognitive correlates.

Both groups exhibited the same pattern of engagement and disengagement of visual attention in the prosaccade task.

They also showed the same impairment in response monitoring during the antisaccade task.

Contrary to predictions of poorer performance of individuals with ASD in ToM tasks, it was observed that both ASD and ADHD groups showed competence in the Triangle Task and the groups could not be differentiated on the basis of their performance. Furthermore, in the Strange Stories task, both group showed relatively poorer understanding of stories with mental content compared to controls, even though it was more pronounced in ADHD group.

In the Cueing task, both groups showed the same pattern of response to different cue types and the lack of sensitivity of the ASD group to social cues could not be confirmed. However, it was found that the ADHD group showed a higher rate of anticipatory saccade than the ASD group.

Finally, in the Sentence Completion task, both the ASD and ADHD groups showed a WCC style by showing tendency for local completions. This is in contrast to the findings of the Booth and Happé study (Booth & Happe, 2010) and queries the specificity of the WCC style to the ASD group.

10.5.3 Findings from the Quantitative Approach

In addition to a categorical approach, the current study adopts a quantitative approach, which assumes that ADHD and ASD are at the extreme ends of continuously distributed traits (as are

the underlying cognitive processes), in order to investigate the predictive accuracy of ASD and ADHD traits for different tasks administered in the study.

Multivariate analysis revealed that performance in the Go/No-Go task, antisaccade task, Strange Stories task, Cueing task, EFT, and Sentence Completion task was only associated with ADHD traits and ASD traits had no explanatory role in the tasks performance.

This pattern of findings, in particular with respect to WCC and ToM accounts, was unexpected and raises some important questions, specifically, whether the tests employed in this battery really index WCC or ToM deficits and whether the previous research reporting WCC and ToM deficits in association with ASD characteristics, should be revisited.

Age and cognitive ability were best at predicting the Triangle Task and Strange Stories outcomes and the Block Design task was mainly influenced by cognitive ability.

10.5.4 Putative Endophenotype Suggested by the Study

The current study had a chance to look at the performance of full-siblings with no clinical diagnosis of ADHD or ASD in order to search for potential endophenotypes.

The initial exploratory study was inadequately powered to identify endophenotypes which are specific to ASD and ADHD. However, the study identified that the cognitive measures that had already shown case-control differences, differentiated siblings as a whole from the controls. It was found that both the antisaccade correction rate and saccade amplitude meet the co-familiality criterion for a broad endophenotype that is shared across the neurodevelopmental disorders of ASD and ADHD. Moreover, the number of local completions in the Sentence Completion task could be considered as a candidate for a broad endophenotype.

These cognitive markers may represent endophenotypes that are shared across ASD and ADHD, perhaps reflecting the shared genetic risk between the two disorders. Further work to test this is clearly warranted.

10.5.5 Suggestions for the Directions of Future Research

As mentioned in the limitations of the study in section 10.4, there are lessons to be learnt from the current study which can be taken into account in the future research to improve the quality of the data.

As mentioned earlier, one of the limitations of the study was the relatively small and unequal sample size which reduced the power of the study to find between group differences which would in turn increase the likelihood of Type II errors when addressing research questions. In order to overcome this limitation, it was planned to expand the current study by recruiting more participants (especially in the pure ASD group and the control group). This is an ongoing work

which has started after the submission of the thesis and would hopefully help to overcome the power issue for future publications.

The other limitation of the study was the rather extensive test battery which might have caused fatigue, especially on the tasks administered more towards the end. Therefore, it was decided to reduce the length of the test battery in the ongoing work in order to increase the quality of the data for future publications. Selected tasks from the main study which showed case-control differences were chosen as potential biomarkers to be further assessed.

It is also suggested that future studies would benefit from considering the following issues: First, it is recommended that the co-occurrence of ADHD and ASD be taken into consideration in order to control for its confounding effect and also to further explore their cognitive profiles.

Second, in term of sample characteristics, administering such an extensive test battery, as used in the present study, in a larger sample with more equal numbers of participants in each group would increase the power to detect group differences. Matching the groups more tightly on their cognitive ability and focusing on a narrower age range would make the interpretation of the findings more straightforward. However, it would provide findings that would be less generalisable.

Moreover, future research should pay careful attention to the selection of the control group, particularly with respect to the presence of ADHD and ASD traits.

Third, the eye movement tasks used in this thesis served to elicit specific oculomotor behaviours in the laboratory. While most types of eye movement under investigation here (reflexive and inhibitory saccade) may be observed in the natural human environment, the experimental tasks that served to study these behaviours in the laboratory (in this thesis as well as in previous studies) are highly operationalised and somewhat artificial. It is suggested that future research design tasks that are more similar to natural situations in order to increase the chance of uncovering subtle differences between groups.

Fourth, this study revealed some developmental progression across the tasks; however, the extent to which the findings on developmental changes can be interpreted and generalised remains unclear and future longitudinal studies are needed to confirm the effects of developmental maturation.

Fifth, previous research has shown different neuroanatomical correlates in brain structure and function of ASD and ADHD groups (Rubia, Halari, Christakou, et al., 2009; Shaw, et al., 2007; Stigler, et al., 2011). It is further recommended that future studies apply neuroimaging methods, comparing neurodevelopmental disorders such as ADHD and ASD, by taking into account their comorbidity, in order to explore whether any differences or similarities exist in the neural

correlates of the two disorders and further explore the neural correlates of comorbid ASD-ADHD.

Sixth, twin and family studies are required to search for a putative endophenotype. It is suggested that future studies focus on larger and more homogenous samples of siblings across the two groups, looking for a candidate endophenotype for each disorder separately, as well as those that span across disorders. From the results so far, it appears that response inhibition and response monitoring should be incorporated in the future studies.

Seventh, genetic linkage findings report that similar areas of the genome might be involved for ASD and ADHD (Smalley, et al., 2002). Moreover, behavioural genetic analysis of both ASD and ADHD showed that there are some common genetic influences operating across autistic traits and ADHD behaviours throughout normal variation and at the extreme (Ronald, et al., 2008). It is suggested that future studies focus on the genetic risk in individuals with a comorbid diagnosis.

Eighth, given the similarities of the cognitive profiles of the ADHD and comorbid groups, it is further suggested that future studies evaluate the medication effect on behavioural and cognitive profiles of individuals with a comorbid diagnosis and assess whether medication has a beneficial effect in this group.

10.5.6 Implications of the Findings

10.5.6.1 Implications for Assessment and Diagnosis

On the basis of the findings, it is suggested that the co-occurrence of ASD and ADHD behaviour reflects a genuine comorbidity between the two disorders. It was revealed that in addition to individuals who were assigned a diagnosis of comorbid ASD-ADHD from the clinics, more individuals were classified in the comorbid group by the research diagnostic assessments. This, therefore, highlights the need to raise awareness of the professionals working in neurodevelopmental clinics and referral centres.

Furthermore, the findings query the rationale for precluding the diagnosis of ADHD in individuals with a diagnosis of ASD and suggest a revision in the current diagnostic criteria.

The findings highlight the importance of considering the co-occurrence of the two disorders both in the clinical and the research settings and the role that cognitive testing may have in the process of diagnosis.

The cognitive biomarkers that have been suggested by this study may have utility in various clinical settings for the assessment and diagnosis of ASD and/or ADHD. For example they can assist as an early pre-symptomatic diagnostic marker, and also as diagnostic tools in complex and borderline cases. However, more research is warranted to find out the sensitivity and specificity of theses markers.

10.5.6.2 Treatment Implications

The investigation of comorbidity is an important issue in the clinic, as accurate diagnosis will consequently lead to more effective treatment strategies. The individuals with a comorbid diagnosis may not benefit fully from the treatment of one condition if the clinician fails to diagnose and treat the ignored comorbid condition.

Moreover, comorbidity is consistently associated with a greater demand for professional help, greater interference with everyday life, a poorer prognosis, and higher suicide rates (Albert, et al., 2008; Schoevers, et al., 2005) which further stresses the importance of recognising the comorbid condition/s.

The use of medication such as the ones which are effectively used for the treatment of ADHD symptoms has been investigated for treating inattention, impulsivity, and overactivity in children with autism. In a study by Santosh (2006), it was found that children with ASD and ADHD respond to stimulant medication equally as well as children with pure ADHD (Santosh, et al., 2006).

However, there are issues with regards to the adverse side effects of stimulant medications as they may worsen the repetitive behaviours of individuals with ASD (Handen, et al., 2000; Santosh, et al., 2006). Therefore, the treatment of ADHD symptoms in individuals with ASD should be carefully considered and in situations like this, the use of non-stimulant medications (e.g. Atomoxetine) is advocated.

The treatment effect could be further incorporated into neuropsychological studies in order to explore whether medication lead to improvement in cognitive task performance.

10.6 Conclusions

In summary, the findings suggest that, even though the core diagnostic criteria of ADHD and ASD are entirely different, the disorders can co-occur, possibly due to shared risk. Furthermore, the study queries the hierarchical approach of the current diagnostic criteria and suggests that the co-occurrence of the two disorders should be taken into consideration both in clinical and research settings.

Understanding the comorbidity better would allow for not only more accurate diagnoses, but also for more effective treatment of children and adolescents with ASD and ADHD.

The neuropsychological findings revealed that some of the cognitive measures assessed the unique cognitive functions specific to one disorder that may represent distinctive aetiological pathways. However, the others tapped into the shared cognitive correlates of ASD and ADHD which may suggest similar aetiological pathways such as shared genetic risk. Poor inhibitory control and a premature style of responding appeared to be candidate biomarkers which

showed some differentiation between the two disorders. In contrast, impairment in response monitoring and a weak central coherence style as observed by a disregard for sentence context were in common to both disorders, showing the shared cognitive correlates.

Comorbidity was not associated with amore impaired cognitive profile than the pure groups. The comorbid ASD-ADHD group showed a response inhibition deficit and premature style of responding similar to the ADHD group, and a relatively poor understanding of the stories with social contents, similar to the ASD group. Moreover, they showed impairments in response monitoring and a weak coherence style in the verbal domain, similar to both groups, which would suggest similar neuropsychological correlates.

The study opened up an avenue for future endophenotype research by showing that the antisaccade correction rate and saccade amplitude meet the co-familiality criterion for a broad endophenotype which is shared across ASD and ADHD. Moreover, the number of local completions in the Sentence Completion task was found to be promising and suggestive of a candidate for a broad endophenotype.

The study has implications for diagnosis and treatment of the two disorders and their comorbidity and suggests that comorbid ASD-ADHD could be a fruitful candidate for further in-depth genetic, neuropsychological and neuroimaging research.

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Appendix A. Criteria for 'Childhood Autism' According to ICD-10

A. Abnormal or impaired development is evident before the age of 3 years in at least one of the following areas:

1. Receptive or expressive language as used in social communication;
2. The development of selective social attachments or of reciprocal social interaction;
3. Functional or symbolic play.

B. A total of at least six symptoms from (1), (2) and (3) must be present, with at least two from (1) and at least one from each of (2) and (3)

1. Qualitative impairment in social interaction is manifested in at least two of the following areas:

a. Failure adequately to use eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction;

b. Failure to develop (in a manner appropriate to mental age, and despite ample opportunities) peer relationships that involve a mutual sharing of interests, activities and emotions;

c. Lack of socio-emotional reciprocity as shown by an impaired or deviant response to other people's emotions; or lack of modulation of behavior according to social context; or a weak integration of social, emotional, and communicative behaviors;

d. Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g. a lack of showing, bringing, or pointing out to other people objects of interest to the individual).

2. Qualitative abnormalities in communication as manifest in at least one of the following areas:

a. Delay in or total lack of, development of spoken language that is not accompanied by an attempt to compensate through the use of gestures or mime as an alternative mode of communication (often preceded by a lack of communicative babbling);

b. Relative failure to initiate or sustain conversational interchange (at whatever level of language skill is present), in which there is reciprocal responsiveness to the communications of the other person;

c. Stereotyped and repetitive use of language or idiosyncratic use of words or phrases;

d. Lack of varied spontaneous make-believe play or (when young) social imitative play

3. Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities are manifested in at least one of the following:

a. An encompassing preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal in content or focus; or one or more interests that are abnormal in their intensity and circumscribed nature though not in their content or focus;

b. Apparently compulsive adherence to specific, nonfunctional routines or rituals;

c. Stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting or complex whole body movements;

d. Preoccupations with part-objects of non-functional elements of play materials (such as their order, the feel of their surface, or the noise or vibration they generate).

C. The clinical picture is not attributable to the other varieties of pervasive developmental disorders; specific development disorder of receptive language with secondary socio-emotional problems, reactive attachment disorder or disinherited attachment disorder; intellectual disability with some associated emotional or behavioral disorders; schizophrenia of unusually early onset; and Rett's Syndrome.

Appendix B. Tasks Order

Tasks Administered	
ADOS	
WASI	(Standard Booklet)
TOWRE	
Motor Task	
Embedded Figures Test	
Planning/Drawing	
Sentence Completion Task	
Alexithymia	(Self Complete)
Triangles	
Non-Word Repetition	
Emotion Labelling	(Recorded by computer)
Emotion Discrimination	(Recorded by computer)
Go/No-Go	(Recorded by computer)
Time Discrimination	(Recorded by computer)
Strange Stories	
Emotion Labelling	(Eye Tracker)
Prosaccade	(Eye Tracker)
Antisaccade	(Eye Tracker)
Social Cueing	(Eye Tracker)

Appendix C. Age, diagnosis, and source of referral for each participant

ID	Age at Referral	Clinical Diagnosis	Borough
1	7y, 9mo	ADHD	Southwark
2	5y	ADHD	Lewisham
3	11y	ADHD	Southwark
4	9y	ASD	Lewisham
5	999	ADHD	Southwark
6	999	ASD	Lewisham
7	5y	ADHD	Southwark
8	6y	ADHD	Lewisham
9	7y	ADHD	Lewisham
10	10y	ADHD+ASD	Lewisham
11	999	ADHD	Lewisham
12	999	ADHD+ASD	Lewisham
13	12y	ASD	Lewisham
14	7y	ASD+ADHD	Lewisham
15	4y	ADHD	Lewisham
16	999	ADHD+ASD	Lewisham
17	4y	ADHD+ASD	Lewisham
18	12y	ASD	PCT-Southwark
19	8y	ADHD	Southwark
20	7y	ASD	Lewisham
21	999	ADHD+ASD	Lewisham
22	7y	ASD	Croydon
23	7y	ASD+ADHD	Lambeth
24	3y	ASD	Lewisham
25	7y	ADHD	Croydon
26	6y	ASD+ADHD	Croydon

ID	Age at Referral	Clinical Diagnosis	Borough
27	6.5y	ASD	Croydon
28	6y	ADHD	Lambeth
29	9y	ADHD	Lewisham
30	8y	ASD	Croydon
31	7y	ASD	Croydon
32	999	ADHD	Southwark
33	7y	ADHD	Croydon
34	10y	ADHD	Croydon
35	7y	ADHD	Lewisham
36	999	ADHD	Lewisham
37	10y	ADHD	Croydon
38	11y	ADHD	Lewisham
39	10y	ASD+ADHD	Croydon
40	12y	ADHD	Southwark
41	9y	ADHD	Lewisham
42	3y	ADHD	Croydon
43	8y	ASD	Croydon
44	8y	ADHD	Croydon
45	2Y	ASD	Croydon
46	10y	ASD	Croydon
47	999	ASD	Lewisham
48	3y	ASD	NAS website
49	10y	ASD	Croydon
50	5.5y	ASD+ADHD	Lewisham
51	2.5y	ADHD+ASD	Croydon
52	7y	ADHD	Southwark
53	8y	ADHD	Lewisham
54	11y	ASD+ADHD	Lewisham

ID	Age at Referral	Clinical Diagnosis	Borough
55	4y	ASD+ADHD	Southwark
56	5y	ASD+ADHD	Croydon
57	9y	ASD+ADHD	Lambeth
58	4y	ASD	Lambeth
59	8y	ASD+ADHD	Lewisham
60	6y	ASD+ADHD	Lewisham
61	7y	ADHD	Southwark
62	7y	ASD	NAS website
63	8y	ASD	Lambeth
64	999	ASD	Lewisham
65	8.5y	ASD+ADHD	Croydon
66	9y	ASD	Croydon
67	2-3y	ASD	Croydon
68	3y	ASD+ADHD	Lewisham
69	6y	ASD	Lewisham
70	10y	ASD	Croydon
71	6y	ASD	Lewisham
72	10y	ASD	Croydon
73	999	ADHD	Croydon
74	6y	ASD+ADHD	Lewisham
75	4y	ASD	Croydon
76	10y	ASD	Lambeth
77	7y	ADHD	Croydon
78	7y	ASD	Croydon
79	10y	ASD	Croydon
80	7y	ADHD	Croydon
81	4y	ASD+ADHD	Lewisham
82	10y	ADHD	Croydon

ID	Age at Referral	Clinical Diagnosis	Borough
83	8y	ADHD	Croydon
84	10y	ASD+ADHD	NAS website
85	8y	ASD	Lewisham
86	10y	ASD	PCT-Southwark
87	13y	ADHD	Croydon
88	6y	ADHD	Croydon
89	3y	ADHD	Croydon
90	5y	ADHD	NAS website
91	10y	ADHD	Croydon
92	10y	ADHD	Southwark
93	9y	ASD	Lewisham
94	6y	ASD	Lewisham
95	5y	ADHD	Croydon
96	13y	ASD	NAS website

999= Missing

Appendix D. Triangle Animations

Scoring verbal descriptions: The verbal descriptions given after each animation were transcribed verbatim and coded in terms of two different dimensions:

Intentionality Score (0 to 5): The Intentionality score reflects the use of mental state terms. The degree of attribution of mental states to the triangles (agents) of the animations was calculated by analysing the content of each description given by the subjects. In the effort to control as much as possible the use of subjective methods in interpreting someone else's language, terminology, idioms and so forth, the analysis was conducted exclusively on the type of verb contained in each sentence used to describe the triangles' actions.

The degree of intentionality reflects in each action was measured with a numerical scale from zero to five. In developing the score, the "intentionality ladder" came into shape, with an agent moving upwards, appreciating step by step both actions, and mental states of another agent. At the bottom of the ladder, where there was no appreciation of another agent, nor actions or mental states (score=0), the agent acts with no intention, and no interaction, randomly, e.g. "moving around", or "floating". A further step up in the ladder (score=1), the agent acts with a purpose, a goal, with no interaction with another agent, e.g. "walking", or "swimming". The following step up (score=2), was when the agent acts with a purpose with another agent, e.g. "fighting" or "following": the actions of the two agents are parallel in time. A further step up (score=3) was when the agent not only interacts with another agent but acts in response to the other's action, e.g. "chasing", or "restraining": the actions of the two agents are sequential in time. Finally, the two steps at the top of the ladder concerned the agent's appreciation of mental states. The lower step (score=4) was when the agent acts in response to a mental state, e.g. "arguing", "wanting" or "encouraging". The upper step (score=5) was when the agent acts with the goal of affecting or manipulating the other agent's mental states, e.g. "pretending", "deceiving" or "coaxing".

Appropriateness score (0-3)

The Appropriateness score measured the understanding of the event depicted in the animations, as intended by the designers. The score, ranging from zero to three, was based on the underlying script for each animation. Details of criteria for rating the appropriateness of each animation are given below. The degree of appropriate description of the animation was calculated by analysing the agents' actions and interactions. For example, an appropriate description (score=3) for the animation where the big triangle persuades the little one to go out, need to convey the idea of little triangle's reluctance to go out and big triangle's attempts to get the little one out, e.g. "persuading" or "coaxing". A less appropriate description (score=2) would focus on one aspect of the story or one character only e.g. 'little one doesn't want to go

out; or, big one is pushing little one to go out'. An inappropriate description (score=1) concerned actions that do not relate to the events or relate to a very minor aspect of the sequence only, e.g. "the two triangles didn't like each other". Finally, when the subject did not provide any description, the score was zero.

Goal-directed Movement Sequences

Leading: (animation with enclosure)

3 = description which conveys the idea of one leading the other or one following the other

2 = description that is related to but somewhat remote from following (e.g. copying; chasing)

1 = action that does not relate to following/leading, or focus solely on a minor aspect of the sequence

0 = Don't Know

Theory of Mind movement sequences

Surprising: (animation with enclosure)

3 = any mention of tricking, surprising, hiding, hide and seek

2 = description which gives part of the story but misses the critical point (see above)

1 = description not related to any of the events in the sequence, or focus solely on a minor part of action (e.g. knocking on the door)

0 = Don't Know

Coaxing: (animation with enclosure)

3 = description that conveys idea of little triangle's reluctance to go out and big triangle's attempts to get the little one out (e.g. persuading, coaxing).

2 = partially correct description focusing on one aspect of the story or one character only,

(e.g. little doesn't want to go out; or, big is pushing little to go out)

1 = actions that do not relate to the events or relate to a very minor aspect of the sequence only (e.g. the two triangles didn't like each other)

0 = Don't Know

Mocking: (animation with enclosure)

3 = description that conveys idea little triangle is copying big one with the intention of not being noticed (e.g. pretending, hiding, being naughty)

2 = partially correct description, (e.g. following, pursuing, copying)

1 = description that does not relate to the events (e.g. big triangle not interested) or relate to a very minor aspect of the sequence only (e.g. little triangle ran away)

0 = Don't Know

Seducing: (animation with enclosure)

3 = description that conveys the little triangle is trapped in and escapes by persuading, tricking the big one (e.g. little convince in a seductive way to let him out)

2 = partial story with minimal action for each character, e.g. little trying to escape

1 = description which is too minimal, e.g. she got out, or unrelated to the sequence.

0 = Don't Know

Appendix E. Strange Stories

10 stories were selected from the 24 set of strange stories designed by Happé (1994).

Practice:

It is Christmas, and Ann's mother takes her to the toy shop. In the toy shop Mr. Jones, Ann's neighbour, is dressed up as Santa Claus, handing out sweets to all the children. Ann runs up to Mr. Jones and says, "Hello. Aren't you Mr. Jones?" Mr. Jones answers, "No, I'm Santa Claus!"

Q: Why does Mr Jones say that?"

ToM Stories

1. Brothers

Simon is a big liar. Simon's brother Jim knows this; he knows that Simon never tells the truth! Now yesterday Simon stole Jim's ping-pong bat, and Jim knows Simon has hidden it somewhere, though he can't find it. He's very cross. So he finds Simon and he says, "Where is my ping-pong bat? You must have hidden it either in the cupboard or under your bed, because I've looked everywhere else. Where is it, in the cupboard or under your bed?" Simon tells him the bat is under his bed.

Q: Why will Jim look in the cupboard for the bat?

- 2 points—reference to Jim knowing Simon lies
- 1 point—reference to facts (that's where it really is, Simon's a big liar) or Simon hiding it without reference to implications of lying
- 0 points—reference to general nonspecific information (because he looked everywhere else)

2. Armies

During the war, the Red army captures a member of the Blue army. They want him to tell them where his army's tanks are; they know they are either by the sea or in the mountains. They know that the prisoner will not want to tell them, he will want to save his army, and so he will certainly lie to them. The prisoner is very brave and very clever; he will not let them find his tanks. The tanks are really in the mountains. Now when the other side ask him where his tanks are, he says, "They are in the mountains".

Q: Why did the prisoner say that?

- 2 points—reference to fact that other army will not believe and hence look in other place, reference to prisoner's realisation that that's what they'll do, or reference to double bluff

- 1 point—reference to outcome (to save his army's tanks) or to mislead them
- 0 points—reference to motivation that misses the point of double bluff (he was scared)

3. Kittens

Jill wanted to buy a kitten, so she went to see Mrs. Smith, who had lots of kittens she didn't want. Now Mrs. Smith loved the kittens, and she wouldn't do anything to harm them, though she couldn't keep them all herself. When Jill visited she wasn't sure she wanted one of Mrs. Smith's kittens, since they were all males and she had wanted a female. But Mrs. Smith said, "If no one buys the kittens I'll just have to drown them!"

Q: Why did Mrs. Smith say that?

- 2 points—reference to persuasion, manipulating feelings, trying to induce guilt / pity
- 1 point—reference to outcome (to sell them or get rid of them in a way which implies not drowning) or simple motivation (to make Jill sad)
- 0 points—reference to general knowledge or dilemma without realization that the statement was not true (she's a horrible woman)

4. Hat

One day Aunt Jane came to visit Peter. Now Peter loves his aunt very much, but today she is wearing a new hat; a new hat which Peter thinks is very ugly indeed. Peter thinks his aunt looks silly in it, and much nicer in her old hat. But when Aunt Jane asks Peter, "How do you like my new hat?", Peter says, "Oh, its very nice".

Q: Why does he say that?

- 2 points—reference to white lie or wanting to spare her feelings; some implication that this is for aunt's benefit rather than just for his, desire to avoid rudeness or insult
- 1 point—reference to trait (he's a nice boy) or relationship (he likes his aunt); purely motivational (so she won't shout at him) with no reference to aunt's thoughts or feelings; incomplete explanation (he's lying, he's pretending).
- 0 points—reference to irrelevant or incorrect facts / feelings (he likes the hat, he wants to trick her)

5. Mrs. Peabody

Late one night old Mrs. Peabody is walking home. She doesn't like walking home alone in the dark because she is always afraid that someone will attack her and rob her. She really is a very nervous person! Suddenly, out of the shadows comes a man. He wants to ask Mrs. Peabody

what time it is, so he walks towards her. When Mrs. Peabody sees the man coming towards her, she starts to tremble and says, "Take my purse, just don't hurt me please!"

Q: Why did she say that, when he only wanted to ask her the time?

- 2 points—reference to her belief that he was going to mug her or her ignorance of his real intention
- 1 point—reference to her trait (she's nervous) or state (she's scared) or intention (so he wouldn't hurt her) without suggestion that fear was unnecessary
- 0 points—factually incorrect / irrelevant answers; reference to the man actually intending to attack her

Physical Stories

1. Armies

Two enemy powers have been at war for a very long time. Each army has won several battles, but now the outcome could go either way. The forces are equally matched. However, the Blue army is stronger than the Yellow army in foot soldiers and artillery. But the Yellow army is stronger than the Blue Army in air power. On the day of the final battle, which will decide the outcome of the war, there is heavy fog over the mountains where the fighting is about to occur. Low-lying clouds hang above the soldiers. By the end of the day the Blue army has won.

Q: Why did the Blue army win?

- 2 points—reference to both weather conditions and either relative ground superiority or inability of other army's planes to be useful in fog (names of armies unimportant)
- 1 point—reference either to weather or relative superiority on ground versus air (because it was foggy); nothing about why weather makes it especially difficult for planes or nothing about planes being affected more than tanks; reference to fog to justify incorrect response (the aeroplanes won because the fog meant they could hide from the tanks)
- 0 points—reference to irrelevant or incorrect information (they won because they had better planes); justifications for why tanks are better than planes

2. Burglar

A burglar is about to break into a jewellers' shop. He skilfully picks the lock on the shop door. Carefully he crawls under the electronic detector beam. If he breaks this beam it will set off the alarm. Quietly he opens the door of the store-room and sees the gems glittering. As he reaches out, however, he steps on something soft. He hears a screech and something small and furry runs out past him, towards the shop door. Immediately the alarm sounds.

Q: Why did the alarm go off?

- 2 points—reference to animal which the burglar disturbed setting off alarm by crossing beam (type of animal unimportant)
- 1 point—reference to burglar setting off alarm (he was startled by the animal so crossed the beam); reference to animal setting off alarm without explaining it crossed the beam (he trod on a cat and it set off the alarm)
- 0 points—reference to irrelevant or incorrect factors (the animal's screech set off the alarm); alternative reasons for alarm going off (a security camera saw him and set the alarm off)

3. Leg

Old Mrs. Robinson is very frail. One day she slips on her icy door step and falls on her side. She gets up right away, although she feels quite bruised and shaken. The next day her leg feels very stiff and she can scarcely walk. She makes her way to the doctors. As soon as the doctor hears about the fall, and sees her swollen side, he says, "Go immediately to casualty". At the casualty department they take an X-ray.

Q: Why did they take an X-ray?

- 2 points—reference to possibility that she has fractured/broken her hip/leg; reference to wanting to know or trying to find out (i.e., "it was broken" is not enough); must refer to fact that X-rays are for broken things or bones (to see if there's any damage to the bone)
- 1 point—reference to general aim (to see what's wrong, because of her fall she might have damaged something) or factually correct (it's bruised and stiff)
- 0 points—reference to irrelevant (because she fell) or incorrect factors (that's what doctors do) or to X-rays being cures themselves (to mend her leg)

4. Light bulbs

John is going shopping. He buys a nice new desk lamp, for his study. He needs a light bulb for his new lamp. He goes from the furniture shop to the electrical shop. In the electrical shop he finds that there are two brands of light bulb of the right kind. Ever-Bright light bulbs cost less in single packs than Light-Right bulbs. However, only Light-Right bulbs come in multi-packs of six. John buys the multi-pack, even though he only needs one bulb.

Q: Why does John buy the Light Right bulbs?

- 2 points—reference to saving money by buying the multipack

- 1 point—reference to convenience of having more bulbs, or future need for more than one bulb; no mention of saving money
- 0 points—reference to irrelevant or incorrect factors (Literite bulbs are brighter)

5. Glasses

Mrs Brown has very poor eyesight. She has only one pair of glasses, which she keeps losing. Today she has lost her glasses again and she needs to find them. She had them yesterday evening when she looked up the television programmes. She must have left them somewhere that she has been today. She asks Ted to find her glasses. She tells him that today she went to her regular early morning swimming class, then to the post office, and last to the flower shop. Ted goes straight to the post office.

Q: Why is the post office the most likely place to look?

- 2 points—reference to post office being place she would most likely use her glasses (to read/write/look at stamps etc); may talk about either putting glasses on or taking them off
- 1 point—plausible alternative reason for being in post office (there are lots of people there, you might have posted them by mistake, people take lost things there)
- 0 points—reference to irrelevant or incorrect factors (that was the last place she went, you can buy glasses at the post office, she needed the glasses to hear better); general factors, nonspecific to post offices

Appendix F. Sentence Completion Task: Stimuli and scoring examples

Sentence stems (in order of administration)	Examples of 2-point local completions with 1-point examples underlined	Examples of 0-point global completions
I was given a pen and ... *		
The sea tastes of salt and ...	pepper / vinegar / sugar / sour	water/ seaweed/ sand/ was cold
Hens lay eggs and ...	bacon / chips / milk / eggs	chicks / have feathers
The woman took the cup and ... *		
You can get burnt by the sun and ...	moon / sea / daughter (son)/ sand / stars / rain	fire / hot water / it hurts
You can feed a child bread and ... *		
Little boys grow up to be men and ...	women / lady	girls grow up to be women/ adults/ granddads
In the sea there are fish and ...	chips	sharks / whales / lots of sea life
In a cave lived a bat and ...	ball	bear/ spiders / a caveman
You can go hunting with a knife and…	fork	gun / bow and arrow
The old shoe-maker mended the shoes and ...	socks / clothes / hats / shirt / laces / slippers	boots / soles / gave them back / cleaned them
The fireman carried the bucket and ...	spade	hose / water / ladder / put out the fire
A vet cares for cats and … *		
The night was black and ...	white / blue	dark/cold / silver (knight) / had a large sword (knight)

* Control items

Appendix G. The tables of key findings representing 95% confidence intervals (CI) for means

Appendix Table G-1: Group Comparisons on Go/No-Go Task measures (CIs presented)

Variable	Group	Mean	SD	Std. Error	95% CI for Mean	
					Lower Bound	Upper Bound
Mean	ASD (N=18)	358.16	68.15	16.06	324.27	392.05
Reaction	ADHD (N=35)	356.39	71.52	12.09	331.82	380.95
Time (msec)	Comorbid (N=41)	343.72	56.09	8.76	326.02	361.42
	Control (N=19)	353.42	71.05	16.30	319.18	387.66
RT Variability	ASD	131.63	44.07	14.30	103.29	159.97
	ADHD	155.87	69.31	10.25	135.55	176.20
	Comorbid	140.02	57.57	9.47	121.24	158.80
	Control	120.47	63.37	13.92	92.88	148.05
Premature	ASD	4.18	4.90	1.15	1.75	6.62
Responses (%)	ADHD	6.44	5.29	0.89	4.62	8.25
	Comorbid	6.80	6.72	1.05	4.68	8.93
	Control	2.85	4.72	1.08	0.58	5.13
Commission	ASD	45.78	17.57	4.14	37.04	54.51
Errors (%)	ADHD	51.18	16.50	2.79	45.51	56.85
	Comorbid	52.59	19.37	3.02	46.47	58.70
	Control	40.74	16.95	3.89	32.57	48.91
Omission	ASD	4.80	4.92	1.16	2.35	7.25
Errors (%)	ADHD	6.39	6.70	1.13	4.09	8.69
	Comorbid	5.23	5.19	0.81	3.59	6.87
	Control	3.83	4.29	0.98	1.77	5.90

Appendix Table G-2: Group comparisons on Prosaccade Task measure (CIs presented)

Variable	Group	Condition	Mean	Std. Error	95% CI	
					Lower Bound	Upper Bound
Prosaccade Latency (msec)	ASD (N=17)	Gap	171.89	8.28	155.47	188.31
		Step	194.82	8.24	178.49	211.16
		Overlap	245.07	13.09	219.12	271.02
	ADHD (N=35)	Gap	159.19	5.77	147.75	170.63
		Step	203.47	5.74	192.09	214.86
		Overlap	259.15	9.12	241.06	277.23
	Comorbid (N=38)	Gap	149.31	5.54	138.32	160.29
		Step	195.25	5.51	184.32	206.18
		Overlap	244.69	8.76	227.33	262.04
	Control (N=22)	Gap	155.37	7.28	140.94	169.81
		Step	186.97	7.24	172.61	201.33
		Overlap	234.26	11.51	211.45	257.07
Prosaccade Velocity (º/s)	ASD	Gap	364.12	13.69	336.99	391.25
		Step	368.94	12.51	344.15	393.74
		Overlap	356.94	13.07	331.03	382.85
	ADHD	Gap	362.78	9.54	343.87	381.69
		Step	364.72	8.72	347.44	382.01
		Overlap	363.20	9.11	345.14	381.26
	Comorbid	Gap	388.06	9.16	369.91	406.20
		Step	391.56	8.37	374.97	408.14
		Overlap	377.32	8.74	359.99	394.65
	Control	Gap	402.34	12.03	378.49	426.19
		Step	408.85	11.00	387.05	430.64
		Overlap	397.90	11.49	375.13	420.68
Prosaccade Amplitude (º)	ASD	Gap	13.21	0.18	12.83	13.60
		Step	13.68	0.14	13.39	13.98
		Overlap	13.37	0.13	13.11	13.64
	ADHD	Gap	13.09	0.18	12.72	13.46
		Step	13.65	0.12	13.40	13.89
		Overlap	13.56	0.13	13.30	13.82
	Comorbid	Gap	13.37	0.15	13.07	13.67
		Step	13.90	0.12	13.66	14.15
		Overlap	13.51	0.14	13.24	13.79
	Control	Gap	13.78	0.23	13.29	14.27
		Step	14.31	0.27	13.75	14.87
		Overlap	14.10	0.20	13.69	14.52

Appendix Table G-2: Group comparisons on Prosaccade Task measure (CIs presented) -Continued

Variable	Group	Condition	Mean	Std. Error	95% CI	
					Lower Bound	Upper Bound
Prosaccade Error Rate (%)	ASD	Gap	2.95	0.94	0.96	4.93
		Step	0.31	0.31	-0.35	0.97
		Overlap	0.00	0.00	0.00	0.00
	ADHD	Gap	0.94	0.56	-0.18	2.07
		Step	0.47	0.26	-0.07	1.01
		Overlap	0.65	0.39	-0.13	1.44
	Comorbid	Gap	1.33	0.52	0.26	2.39
		Step	0.82	0.67	-0.54	2.19
		Overlap	0.27	0.27	-0.29	0.82
	Control	Gap	0.90	0.69	-0.52	2.33
		Step	0.45	0.32	-0.20	1.10
		Overlap	0.00	0.00	0.00	0.00
Antisaccade Correction Rate (%)	ASD	Gap	79.58	6.39	66.03	93.14
		Step	84.45	4.94	73.98	94.91
		Overlap	72.67	7.80	56.15	89.20
	ADHD	Gap	82.53	3.80	74.81	90.25
		Step	74.23	4.12	65.86	82.59
		Overlap	65.39	5.44	54.33	76.45
	Comorbid	Gap	83.45	3.10	77.18	89.73
		Step	82.35	2.66	76.96	87.75
		Overlap	72.21	4.46	63.17	81.24
	Control	Gap	96.64	1.15	94.26	99.03
		Step	90.10	2.56	84.78	95.41
		Overlap	87.12	3.42	79.93	94.32

Appendix Table G-3: Group comparisons on Triangle Task measure (CIs presented)

Variable	Group	Mean	SD	95% CI for Mean	
				Lower Bound	Upper Bound
GD Intentionality	ASD (N=18)	2.06	0.64	1.74	2.37
	ADHD (N=34)	2.26	0.83	1.98	2.55
	Comorbid (N=38)	2.39	1.13	2.02	2.77
	Control (N=20)	2.10	1.02	1.62	2.58
GD Appropriateness	ASD	2.00	0.84	1.58	2.42
	ADHD	1.91	0.75	1.65	2.17
	Comorbid	1.84	0.75	1.59	2.09
	Control	1.95	0.83	1.56	2.34
ToM Intentionality	ASD	3.25	0.59	2.96	3.54
	ADHD	3.35	0.74	3.09	3.61
	Comorbid	3.20	0.74	2.95	3.44
	Control	3.26	0.74	2.92	3.61
ToM Appropriateness	ASD	1.54	0.44	1.32	1.76
	ADHD	1.66	0.51	1.49	1.84
	Comorbid	1.61	0.45	1.46	1.76
	Control	1.76	0.46	1.55	1.98

Appendix Table G-4: Group comparisons on Strange Stories Task measure (CIs presented)

Variable	Group	Mean	SD	95% CI for Mean	
				Lower Bound	Upper Bound
Mental State Stories	ASD (N=13)	6.46	2.85	4.74	8.18
	ADHD (N=20)	5.25	2.55	4.06	6.44
	Comorbid (N=30)	6.40	2.34	5.53	7.27
	Control (N=19)	7.63	2.36	6.49	8.77
Physical Stories	ASD	5.08	2.50	3.57	6.59
	ADHD	5.24	2.49	4.11	6.37
	Comorbid	5.13	1.91	4.42	5.85
	Control	5.74	2.77	4.40	7.07

Appendix Table G-5: Group comparisons on Cueing Task measure (CIs presented)

Variable	Group	Cue Type	Congruency	Mean	Std. Error	95% CI Lower Bound	95% CI Upper Bound
Saccade Latency (msec)	ASD(N=17)	Gaze	Congruent	247.56	16.29	215.26	279.86
			Incongruent	235.36	11.74	212.08	258.64
		Arrow	Congruent	241.55	13.76	214.28	268.82
			Incongruent	250.63	12.92	225.02	276.25
	ADHD(N=34)	Gaze	Congruent	257.14	11.52	234.30	279.98
			Incongruent	237.35	8.30	220.89	253.81
		Arrow	Congruent	217.04	9.73	197.76	236.32
			Incongruent	259.36	9.14	241.25	277.48
	Comorbid(N=38)	Gaze	Congruent	261.16	10.90	239.55	282.76
			Incongruent	254.04	7.85	238.47	269.61
		Arrow	Congruent	222.29	9.20	204.05	240.53
			Incongruent	269.58	8.64	252.44	286.71
	Control(N=22)	Gaze	Congruent	257.38	14.32	228.98	285.77
			Incongruent	237.97	10.32	217.51	258.44
		Arrow	Congruent	222.08	12.09	198.11	246.06
			Incongruent	251.87	11.36	229.35	274.39
Saccade Amplitude (º)	ASD	Gaze	Congruent	13.85	0.24	13.38	14.32
			Incongruent	14.11	0.19	13.74	14.48
		Arrow	Congruent	13.49	0.22	13.04	13.93
			Incongruent	13.96	0.27	13.42	14.50
	ADHD	Gaze	Congruent	13.66	0.17	13.32	13.99
			Incongruent	13.90	0.13	13.64	14.16
		Arrow	Congruent	13.12	0.16	12.80	13.43
			Incongruent	13.99	0.19	13.61	14.37
	Comorbid	Gaze	Congruent	13.75	0.16	13.44	14.07
			Incongruent	14.15	0.12	13.90	14.40
		Arrow	Congruent	13.40	0.15	13.10	13.70
			Incongruent	14.15	0.18	13.79	14.51
	Control	Gaze	Congruent	14.26	0.21	13.84	14.67
			Incongruent	14.34	0.16	14.02	14.66
		Arrow	Congruent	13.97	0.20	13.58	14.36
			Incongruent	14.72	0.24	14.25	15.20
Anticipatory Saccade (%)	ASD	Gaze	Congruent	6.05	3.21	-0.32	12.42
			Incongruent	9.91	3.55	2.88	16.94
		Arrow	Congruent	9.86	3.47	2.98	16.74
			Incongruent	15.05	3.90	7.32	22.78
	ADHD	Gaze	Congruent	16.27	2.27	11.76	20.78
			Incongruent	16.95	2.51	11.97	21.92
		Arrow	Congruent	17.11	2.45	12.24	21.97
			Incongruent	24.07	2.76	18.60	29.53
	Comorbid	Gaze	Congruent	12.35	2.15	8.09	16.62
			Incongruent	14.74	2.37	10.04	19.45
		Arrow	Congruent	18.35	2.32	13.74	22.95
			Incongruent	17.64	2.61	12.47	22.81
	Control	Gaze	Congruent	6.43	2.83	0.82	12.03
			Incongruent	11.18	3.12	5.00	17.36
		Arrow	Congruent	12.69	3.05	6.64	18.73
			Incongruent	16.19	3.43	9.40	22.99

Appendix Table G-6: Group comparisons on Cueing Task measure (CIs presented)-Continued

Variable	Group	Cue Type	Congruency	Mean	Std. Error	95% CI	
						Lower Bound	Upper Bound
Correction Rate in the Cue Period (%)	ASD	Gaze	Congruent	10.71	13.16	-15.70	37.13
			Incongruent	12.50	10.56	-8.69	33.69
		Arrow	Congruent	22.08	12.25	-2.52	46.68
			Incongruent	2.50	8.69	-14.94	19.94
	ADHD	Gaze	Congruent	8.67	5.61	-2.59	19.94
			Incongruent	13.20	4.50	4.17	22.24
		Arrow	Congruent	16.43	5.23	5.94	26.92
			Incongruent	7.91	3.70	0.47	15.35
	Comorbid	Gaze	Congruent	22.36	5.88	10.55	34.18
			Incongruent	13.82	4.72	4.34	23.30
		Arrow	Congruent	18.04	5.48	7.04	29.04
			Incongruent	15.08	3.89	7.28	22.88
	Control	Gaze	Congruent	18.52	8.77	0.91	36.13
			Incongruent	15.61	7.04	1.48	29.74
		Arrow	Congruent	13.27	8.17	-3.13	29.67
			Incongruent	22.35	5.79	10.72	33.97

Appendix Table G-7: Group comparisons on Embedded Figure Task measure (CIs presented)

Variable	Group	Mean	SD	Std. Error	95% CI	
					Lower Bound	Upper Bound
Accuracy	ASD (N=19)	89.82	11.19	2.57	84.43	95.22
	ADHD (N=35)	92.19	7.32	1.24	89.68	94.70
	Comorbid (N=42)	89.68	11.61	1.79	86.06	93.30
	Control (N=19)	90.88	7.44	1.71	87.29	94.46
RT1: to Correct Responses (Sec)	ASD	12.02	5.46	1.25	9.39	14.66
	ADHD	10.77	3.77	0.64	9.48	12.07
	Comorbid	10.62	4.70	0.73	9.15	12.09
	Control	12.97	5.06	1.16	10.53	15.41
RT to all	ASD	16.75	7.81	1.79	12.98	20.51
	ADHD	14.61	5.07	0.86	12.87	16.35
	Comorbid	15.27	8.06	1.24	12.76	17.78
	Control	17.13	6.42	1.47	14.04	20.22
False Claim	ASD	5.32	2.93	0.67	3.91	6.73
	ADHD	9.40	6.26	1.06	7.25	11.55
	Comorbid	9.79	5.61	0.87	8.04	11.53
	Control	6.74	4.74	1.09	4.45	9.02

Appendix Table G-8: Group comparisons on Block Deign Task measure (CIs presented)

Variable	Group	Mean	SD	Std. Error	95% CI Lower Bound	95% CI Upper Bound
Number of Correct Designs	ASD (N=19)	8.74	3.00	0.69	7.29	10.18
	ADHD (N=35)	7.66	2.97	0.50	6.64	8.68
	Comorbid (N=42)	8.17	2.66	0.41	7.34	9.00
	Control (N=19)	9.21	2.86	0.58	8.00	10.42
BD Tscore	ASD	54.79	10.49	2.41	49.74	59.84
	ADHD	49.26	9.65	1.63	45.94	52.57
	Comorbid	54.24	9.50	1.47	51.28	57.20
	Control	58.63	9.32	1.90	54.69	62.56

Appendix Table G-9: Group comparisons on Sentence Completion Task measure (CIs presented)

Variable	Group	Mean	SD	Std. Error	95% CI Lower Bound	95% CI Upper Bound
Number of Local Completions	ASD (N=19)	1.74	1.85	0.42	0.84	2.63
	ADHD (N=35)	1.47	1.35	0.23	1.00	1.94
	Comorbid (N=42)	1.48	1.64	0.25	0.96	1.99
	Control (N=19)	0.45	0.69	0.15	0.13	0.77
Completion Score	ASD	16.00	3.64	0.83	14.25	17.75
	ADHD	16.62	2.77	0.48	15.65	17.59
	Comorbid	16.55	3.41	0.53	15.49	17.61
	Control	18.65	1.76	0.39	17.83	19.47